A Case of Crossed Logopenic Primary Progressive Aphasia in a Dextral Patient with Underlying Frontotemporal Dementia

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Abstract:
A 61-year-old dextral woman was admitted to the hospital with difficulty finding words. Neurological examinations confirmed that her speech was affected by frequent pauses and occasional phonological paraphasia without cognitive deficits. We detected atrophy, hypoperfusion, and hypometabolism in the right perisylvian and parietal regions, expanding to the right anterior temporal lobes and right inferior frontal gyrus (opercular region) by magnetic resonance imaging, single-photon emission computed tomography, and fluorodeoxyglucose-positron emission tomography (PET), respectively. Amyloid-PET did not identify the accumulation of amyloid beta (Aβ) in the bilateral cerebral cortices. We herein report a case of crossed aphasia with Aβ-negative logopenic primary progressive aphasia that was likely the result of frontotemporal lobar degeneration.

Key words: logopenic primary progressive aphasia, crossed aphasia, dextral, amyloid positron emission tomography, frontotemporal dementia, amyloid beta

Introduction
The term “aphasia” is used to describe a group of conditions characterized by language impairments, including speech production and comprehension and the ability to read and write. Aphasia occurs as a result of damage to the language-dominant hemisphere of the brain following brain injury or stroke and is most prevalent in elderly patients. Primary progressive aphasia (PPA) is a rare neurological syndrome characterized by gradual, progressive language impairments in the absence of other forms of cognitive dysfunction (1). The criteria for the diagnosis of PPA consist of the following: 1) the most prominent clinical feature is difficulty with language; 2) these deficits are the principal cause of impaired activities of daily living; and 3) aphasia should be the most prominent deficit at symptom onset and during the initial phases of the disease (1). In contrast to other types of aphasia, PPA is caused by atrophy of the frontal, temporal, or parietal lobe in the language-dominant hemisphere of the brain, often as a result of an underlying neurodegenerative disease.

Gorno-Tempini et al. described three clinical variants of PPA according to the language phenotype: nonfluent/agrammatic variant PPA (nvPPA or PNFA), semantic variant PPA (svPPA), and logopenic variant PPA (lvPPA or LPA) (2). In nvPPA or PNFA, patients develop progressive problems in speech production, resulting in articulation and phonemic breakdown. In svPPA, patients have difficulties understanding the meaning of words and finding words or names for familiar people and objects. Based on its pathology, svPPA is considered a subtype of frontotemporal dementia. Finally, in lvPPA or LPA, individuals have well-articulated, grammatically correct speech and single-word comprehension, but speech is slow and hesitant due to difficulties in recalling the correct words. Patients with LPA typically retain the

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ability to recall the meaning of words, and their speech is fluent when familiar words are used (2). In pathological studies, Pittsburgh compound B (PiB)-based amyloid beta (Aβ) imaging and cerebrospinal fluid biomarker analyses (such as tau and Aβ) have shown that the majority of cases with LPA share clinical features with Alzheimer’s disease (3-13).

Crossed aphasia was first described as a language disorder in dextral (right-handed) patients, secondary to a unilateral right hemispheric lesion (13, 14). Dextral subjects show a language function that is lateralized to the left hemisphere. The major cause of aphasia in dextral subjects is a left hemispheric lesion (13, 14). Dextral subjects show a language function that is lateralized to the left hemisphere.

We herein report a case of crossed Aβ-negative LPA in a dextral patient.

## Case Report

A 61-year-old dextral woman was admitted to our hospital due to difficulty finding words. The patient had no relevant medical history and there was no family history of left-handedness or neurodegenerative disorders. The patient had graduated from high school with no intellectual disability. Family members noted that the patient had exhibited problems naming familiar daily objects for approximately three years before admission.

On admission, the patient was alert, with a body temperature of 36.2°C, blood pressure of 124/82 mmHg, and pulse of 69 beats per min. We detected no abnormalities in our examinations of the heart, lungs, and abdomen. Furthermore, a neurological examination revealed no focal neurological deficits, and the patient had no memory impairments. Apraxia and agnosia were not noted. Prosopagnosia, as assessed by the Visual Perception Test for Agnosia (17), was not present. We found no notable deviations on a blood analysis. The patient produced a perfect score (+10) upon completing a Japanese version of the FLANDERS handedness questionnaire (17), indicating that she was strongly right-handed.

We evaluated aphasia using the Standard Language Test of Aphasia (SLTA) for Japanese speakers (17) (Fig. 1). Overall, her spontaneous speech was relatively slow, with frequent pauses due to difficulty finding the appropriate words. Her produced speech showed no grammatical errors, anarthria (an inability to produce clear articulate speech), or dysarthria (slurred speech due to a motor speech disorder).

The patient answered 18 out of 20 questions on confrontation naming in the SLTA, although she took some time to provide 2 of the correct answers. The patient had impaired spontaneous speech and confrontation naming, with particular difficulties in finding low-frequency words. Single-word and short-sentence repetition with the exclusion of one instance of phonological paraphasia was nearly intact in the SLTA, but the repetition of longer complex sentences was impaired. Explaining the comic strip provided in the SLTA took 48 seconds. In her description of the comic, all basic words were included, but only half of the related words were included. In addition, one instance of phonological...
paraphasia and two occurrences of verbal paraphasia were recognized. Although a pause occurred once while explaining the comic strip, interjection was found frequently (nine times). Finally, when explaining the comic strip, occasional phonological paraphasia and misused Japanese postpositional particles were apparent. Regarding phonological paraphasia (when a word is substituted with a non-word that preserves at least half of the segments of syllables of the intended word), the patient would say “tukimi” instead of “tumiki” (meaning block in Japanese). Her auditory processing and reading skills were almost fully preserved. Although her writing skills were also almost fully preserved, one instance of paragraphia and misspelling occurred.

We next performed a series of cognitive examinations. The patient scored 29 out of 30 points, which is within normal range, in both Mini-Mental State Examination (18) (1-point deduction for repetition of a sentence) and Hasegawa Dementia Scale-Revised (19) (1-point deduction for a backward digit span). She scored 11 out of 18 points in the Frontal Assessment Battery (20), based on the following individual scores: Similarities, 2/3; Lexical fluency, 1/3; Motor series, 1/3; Conflicting instruction, 3/3; Go-No-Go, 1/3; and Prehension behavior, 3/3.

In the Raven’s Colored Progressive Matrices (21) non-verbal test of abstract reasoning, the patient scored 33 out of 36 points, based on the following scores: Set A, 12/12; Set AB, 11/12; and Set B, 10/12. The average score in this test for a woman aged 60 years is 29.2 points; thus, our patient provided an above average score. On the Kohs block-design test (22), her intelligence quotient was 124. These results indicated preserved visuospatial abilities. The results of both of these tests indicated that the patient’s visuospatial abilities were intact.

Magnetic resonance imaging (MRI) of the brain did not provide clear evidence of ischemic changes, basal ganglia degeneration, or amyloid angiopathy. A further analysis with a voxel-based specific regional analysis system for Alzheimer’s disease (VSRAD) (23) revealed significant atrophy in the medial temporal lobe, including the entorhinal cortex, amygdala, and hippocampus. Specifically, we found evidence of atrophy in the medial temporal lobe, including the entorhinal cortex, amygdala, and hippocampus. Brain atrophy detected by MRI was predominantly in the right hemisphere, affecting the following regions: superior temporal gyrus, inferior parietal lobules, anterior temporal lobes, and inferior frontal gyrus (opercular part). Slight atrophy was identified in the left anterior temporal lobes (Fig. 2).

We also performed single-photon emission computed tomography (SPECT) using ""Tc-ethyl-cysteinate dimer (""Tc-ECD), with an evaluation using an easy Z-score imaging system (eZIS). We noted a decreased perfusion in the following regions: right superior and inferior parietal lob-
Figure 3. Single-photon emission computed tomography (SPECT). (A) SPECT images showing a decrease in the cerebral blood flow in the right fronto-temporo-parietal lobes. (B) SPECT images analyzed with an easy Z-score imaging system (eZIS), showing a decrease in the cerebral blood flow in the right supramarginal and angular gyri, superior and inferior parietal lobules, left inferior frontal gyrus (opercular part), right medial frontal gyrus, bilateral superior frontal gyrus, left inferior frontal gyrus (opercular part), left precuneus and cuneus, and left occipital gyri (Fig. 3). Overall, perfusion was decreased more on the right side than on the left side.

Finally, we performed amyloid positron emission tomography (PET) and fluorodeoxyglucose (FDG)-PET imaging. We found no Aβ accumulation in the bilateral cerebral cortices by amyloid PET, indicating the absence of this hallmark of Alzheimer’s disease (Fig. 4a). Conversely, we detected hypometabolism using FDG-PET in the following regions: right superior temporal and middle temporal gyri, right supramarginal and angular gyri, right anterior temporal lobes, and left inferior frontal gyrus (opercular part) and right middle frontal and superior frontal gyri. Slight hypometabolism was also detected in the left inferior (opercular) frontal gyrus (Fig. 4b). A visual inspection of a [123I]-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) SPECT scan revealed a normal FP-CIT uptake and striatal uptake ratio (SUR), as determined using DaTQUANT™ (Fig. 5).

Discussion

To make a clinical diagnosis of LPA, the following core features must be present: impaired single-word retrieval in spontaneous speech and naming and impaired repetition of sentences and phrases. In addition, at least three of the following features must also be present: speech (phonologic) errors in spontaneous speech and naming; spared single-word comprehension and object knowledge; spared motor speech; and absence of frank agrammatism (the omission and/or substitution of grammatical morphemes with associated grammatical errors). To support a diagnosis of LPA, MRI analyses may indicate predominant left posterior perisylvian or parietal atrophy, and/or SPECT or PET analyses may reveal predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism.

Our case displayed the clinical features of LPA and crossed aphasia, based on her being strongly right-handed (according to the FLANDERS handedness questionnaire and medical and family history) and abnormal cerebral imaging predominantly in the right cerebral hemisphere.
**Figure 4.** Amyloid positron emission tomography (PET) images and fluorodeoxyglucose-PET images. (A) Amyloid-PET images using Pittsburgh compound B. No accumulation of amyloid beta was evident in the bilateral cerebral cortices. (B) Fluorodeoxyglucose-PET images analyzed with the easy Z-score imaging system (eZIS) showing glucose hypometabolism in the right superior temporal and middle temporal gyri, right supramarginal and angular gyri, right anterior temporal lobes atrophy, right inferior frontal gyrus (opercular part) and the right middle frontal and superior frontal gyri, and slight hypometabolism in the left inferior frontal gyrus (opercular part).

**Figure 5.** $^{[123]}$I-2β-Carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) SPECT images. The striatal uptake ratio (SUR) was 2.28 (normal range 1.95 ± 0.33) in the right striatum and 2.28 (normal range 1.98 ± 0.35) in the left striatum using DaTQUANT™. This analysis indicated that the SUR of the patient was within the normal range.
We are aware of four previous cases of LPA with crossed aphasia (24-27). These cases showed right hemispheric atrophy and hypometabolism or hypoperfusion. Of these cases, two exhibited the accumulation of Aβ by amyloid-PET (26, 27), which is indicative of Alzheimer’s disease as the underlying pathology. Amyloid-PET was not performed on the other two cases (24, 25). As we did not detect any Aβ accumulation by amyloid-PET in our patient, we consider this to be the first case report of crossed aphasia with Aβ-negative LPA.

Patients with LPA show atrophy and metabolic disturbances in the left parietal temporoparietal junction, as determined by cerebral imaging. These characteristics are similar to those reported in patients with Alzheimer’s disease (28). As such, many clinicians have inferred that Alzheimer’s disease is the underlying cause of LPA (4-11). Several studies have performed amyloid-PET to assess the Aβ accumulation directly in patients with LPA (4-6, 8-11), and comparisons between Aβ-positive and Aβ-negative LPA have been made (10, 11). Whitwell et al. reported that atrophy (as assessed by MRI) and hypometabolism (as assessed by FDG-PET) were restricted to the left hemisphere in a PiB-negative lvPPA group. In addition, this report showed significantly greater asymmetry scores in the lateral temporal lobe, hippocampus, and temporal pole, and in the precuneus and medial frontal lobe on FDG-PET than in a PiB-positive lvPPA group (10). In our case, atrophy (as detected by MRI) and hypoperfusion or hypometabolism (as detected by FDG-PET) were confined to the right hemisphere in the temporal lobe, right supramarginal and angular gyri, and inferior frontal gyrus (opercular part).

The abnormality in the right hemisphere of our case was similar to that in the left hemisphere reported by Whitwell et al. To support a diagnosis of LPA, imaging analyses may indicate predominant left posterior perisylvian or parietal atrophy by MRI and hypoperfusion or hypometabolism by SPECT or PET. However, Whitwell et al. detected atrophy and hypoperfusion or hypometabolism in the left temporoparietal region, extending to the left frontal lobe, in both PiB-positive and PiB-negative LPA. Similarly, Matías-Guixé et al. reported hypometabolism in the left temporoparietal region, extending to the anterior temporal and basal frontal regions, with greater frequency in Aβ-negative cases than in Aβ-positive cases (11). Therefore, it is possible that the abnormality causing LPA is not confined to the posterior perisylvian or parietal lobe but in fact spread more widely.

Interestingly, our case exhibited abnormalities extending to the anterior temporal and inferior frontal (opercular) gyrus, which is more characteristic of PNFA and svPPA than LPA. However, it was reported recently that FDG-PET was not clinically effective at differentiating between PPA variants (29). nfvPPA and svPPA are well recognized as the most common pathologies of FTLD (30). Recently, several studies have identified signs of FTLD in Aβ-negative LPA (8, 11, 12), and Aβ-negative LPA is considered to be a part of the spectrum of FTLD (12). Therefore, the language defects in our case may be the result of FTLD.

CROSSED APHASIA IN DEXTRALS

CROSSED APHASIA IN DEXTRALS (CAD) has been reported mainly as a cerebrovascular disease (13, 14), and only a few cases with PPA have been reported (24-27, 33). Therefore, historically, reports on CAD have mainly consisted of examinations of subjects with CAD due to cerebrovascular disease. There are two main types of CAD: mirror image CAD and anomalous image CAD (31). The mirror image type is aphasia that corresponds to a left hemisphere lesion, while the anomalous image type is aphasia that does not correspond to a left hemisphere lesion. Brown et al. hypothesized that the difference between the two types was caused by the degree of dominance establishment present at the moment of brain damage (32). In a report of CAD caused by a cerebrovascular disorder, 23 of 49 cases were mirror image CAD, with this type being approximately twice as frequent as anomalous image CAD (13).

Given the signs of crossed aphasia in our dextral patient, we also hypothesize that the language-dominant hemisphere of this patient is located in the right hemisphere because of the prominent damage to this hemisphere. This concept remains to be confirmed by a functional MRI (fMRI) activation analysis, which was unavailable during our treatment of this patient. A recent study by Spinelli et al. showed that fMRI conducted during a naming task identified bilateral language activation in a case of crossed PNFA with prominent damage to the right hemisphere (31). This finding implies pre-morbid bilateral language lateralization. Cabrera-Martín et al. reported a similar activation pattern in both hemispheres, as detected by fMRI, in a case of crossed LPA (26). Therefore, fMRI analysis can be used to reveal language lateralization in detail.

The core features of LPA are impaired single-word retrieval in spontaneous speech and naming and impaired repetition of sentences and phrases. However, difficulty finding words is present in both PNFA and SD, which can make classification problematic. PPA as one of the three clinical variants and cases with unclassifiable PPA do exist.

Montembeault et al. reported that many factors may be associated with unclassifiable PPA cases (30). For example, similar symptoms might be due to the distinct causes between the underlying PPA variant (30), and thus it may not be possible to classify all cases clearly as variants of PPA. Although our case met the criteria for LPA, the diagnosis may change depending on the progression of her symptoms, which were mild at the initial presentation. Therefore, this case will require careful follow-up, as changes may become evident as the disease progresses.

In summary, our patient exhibited Aβ-negative LPA with crossed aphasia. We must now follow this patient longitudinally and carefully observe the clinical symptoms and pathologic changes detectable by cerebral imaging.

The authors state that they have no Conflict of Interest (COI).

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