Primary progressive apraxia of speech (AOS) in a patient with Pick’s disease with Pick bodies: a neuropsychological and anatomical study and review of literatures

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A 56-year-old right-handed man suffered from progressive apraxia of speech (AOS), characterized by agrammatism and buccofacial apraxia. He also became mute at the later stages of the disease progression. At autopsy, the left precentral gyrus, pars opercularis, and hippocampus showed severe atrophy. Pick bodies and Pick cells were observed. In this report, we also review previous case reports of AOS. Pick’s disease is among the most commonly associated of the major diseases. Brain lesions associated with AOS may be found in regions such as the precentral gyrus and the pars opercularis in the left hemisphere.

Keywords: Apraxia of speech (AOS); Pick’s disease; Pick bodies (PB); Precentral gyrus; Pars opercularis.

Apraxia of speech (AOS) is a rare disturbance in speech output that does not involve impairment of auditory or reading comprehension or writing (Darley, 1968). This disorder usually results from strokes (Lecours & Lhermitte, 1976). Aside from a seminal review on AOS in patients with neurodegenerative disorders (Duffy, 2006), only a few case reports have documented AOS diagnoses and pathological evaluations in sufficient clinical detail (Broussolle et al., 1996; Fukui, Sugita, Kawamura, Shiota, & Nakano, 1996; Sakurai et al., 1998).

In this paper, we describe the case of a patient who clinically presented with progressive AOS and was pathologically confirmed as having Pick’s disease (PiD) with Pick bodies (PB) (PiDPB). In addition, we review previously reported cases on the basis of two main criteria. First, sufficient clinical descriptions were required to allow our neuropsychologist (M.B.) to determine whether the speech disorder described above was indeed AOS. Second, there needed to be sufficiently detailed pathological examinations performed to determine the pathological diagnosis and the anatomical distributions of lesions in affected brain regions. The purpose of this study was to determine the clinico-anatomical relationship between AOS and the original lesion responsible for AOS. Furthermore, we discuss the underlying pathological spectrum of AOS.

CASE REPORT

A 56-year-old right-handed Japanese male office worker often repeated the word ‘well’ in...
conversations in 1985. He had no prior medical history of neurological diseases, nor did his family. He noted difficulties in finding words and in ‘expressing his thoughts’. In April 1991, his first physical examination revealed no remarkable findings. Neurological and neuropsychological examinations showed that his speech was not effortful, but was slightly slow, and he frequently stopped talking to search for speech sounds. His speech was agrammatic, with marked ‘phonemic paraphasia’, and his vowels too were either substituted, omitted, added, or distorted. It was difficult to determine whether these errors were phonological or phonetic (Code, 1998). His speech was so dysprosodic that it gave an impression of having a ‘foreign accent’, although not full-blown. This articulatory impairment featured inconsistent distortions, omissions, and substitutions of phonemic realization, which are characteristics of AOS (Code, 1998; Sugishita et al., 1987). The patient exhibited a mild writing disturbance, which consisted of phonemic paragraphia. His examination results, obtained from the Japanese version of the Western Aphasia Battery (WAB), are shown in Table 1. He scored a 160/165 on the Token Test. His score on the Standard Language Test for Aphasia (SLTA) also showed impaired repetition and dictation of sentences, whereas his auditory and written comprehension and his dictation of single words were relatively well preserved. These results suggest that the cardinal speech problem was an impairment of phonetic production, and his language profile at this stage indicated AOS with agrammatism. His performance on the formal intelligence test was slightly poor, mainly owing to his language impairment. His performance IQ was determined using the Wechsler Adult Intelligence Scale-Revised (WAIS-R), and he scored a 96. The Rey’s Complex Figure Test, the Illinois Test of Psycholinguistic Abilities (ITPA), and the Motor Sequence Test were also performed. The results from these exams showed that his intelligence was almost normal, without any memory disturbance. The patient also had buccofacial apraxia. Routine laboratory tests showed mostly unremarkable findings, except for a chronic hepatitis C viral infection. A magnetic resonance imaging (MRI) study demonstrated an enlargement of the left Sylvian fissure and atrophy of the left superior temporal gyrus, left central operculum, and insular cortex (Figure 1). Single-photon emission computed tomography (SPECT) showed abnormalities of the left frontotemporal regions, particularly in the perisylvian region (Figure 2). Serial evaluations using the Japanese version of the WAB from 1992 to 1997 revealed that his auditory and reading comprehension remained relatively well preserved, whereas his repetition, word fluency, and writing had progressively worsened (Table 1). However, there was no apparent detection of a deterioration of personality or intelligence. In July 1997, the patient exhibited severe AOS, and he became functionally mute. He also presented with both ideomotor and ideational apraxia. In December 1997, his bradykinesia and dysphagia had progressively worsened; however, he was independent in his daily living until July 1998, when he was admitted to our department for aspiration pneumonia. His neurological examination indicated that he was mute because he was only capable of producing the ‘ouch’ or ‘uhh-uhh’ sounds; however, he remained ambulant, recognized people, and gave the clinical impression of being able to understand simple questions. He remained polite to the hospital staff and exhibited appropriate behavior. Owing to the progression of his liver dysfunction and frequent aspiration pneumonia, he died in February 1999 at the age of 69, 13 years after the onset of the disease.

| TABLE 1 | Patient scores in the Japanese version of the Western Aphasia Battery (WAB) |
|---------|---------------------|-----|-----|-----|
| Time    | June 1991 | Oct. 1992 | Nov. 1994 | May. 1997 |
| WAB subscale |  |  |  |  |
| Spontaneous speech |  |  |  |  |
| Information | 8 | 1 | 0 | 0 |
| Fluency | 8 | 1 | 0 | 0 |
| Comprehension | 9.25 | 9.55 | 7.0 | 5.2 |
| Repetition | 7 | 2.6 | 0 | 0 |
| Naming | 5.5 | 1.1 | 0 | 0 |
| Reading | 8.3 | 7.0 | 3.15 | 2.1 |
| Writing | 7.5 | 6.55 | 4.55 | 2.75 |
| Praxis (right) | 8.8 | 8.5 | 7.56 | 3.0 |
| Praxis (left) | 8.8 | 8.5 | 7.56 | 3.33 |
| Construction | 8 | 8.8 | 6.4 | 7.5 |
| AQ | 75.1 | 30.5 | 14.0 | 10.4 |
| CQ – right hand | 79.4 | 55.65 | 44.66 | 25.75 |
| CQ – left hand | 79.4 | 55.65 | 44.66 | 26.08 |

Note: AQ, Aphasia Quotient; CQ, Cortical Quotient.
Figure 1. Magnetic resonance (MR) T1-weighted images taken in May 1991. The right side of the brain is indicated by an R. MR images show the enlargement of the left Sylvian fissure and atrophy of the superior temporal gyrus, operculum, and insular cortex in the left hemisphere.

Figure 2. Single-photon emission computed tomography (SPECT) images taken in May 1991. The left side of the brain is indicated by an L, and the right side by an R. SPECT images reveal decreases in cerebral blood flow in the left frontotemporal lesions, particularly in the perisylvian lesions.

NEUROPATHOLOGICAL EXAMINATION

The fresh brain weighed 1068 g. A gross external examination (Figure 3A–D) revealed that the left hemisphere showed severe focal atrophy of the pars opercularis, the lower part of the precentral gyrus, the anterior part of the temporal lobe, and the superior frontal gyrus. In contrast, the left middle and inferior temporal gyri were relatively well preserved. In the right hemisphere, the medial part of the temporal lobe was mildly atrophic, and the superior frontal gyrus showed moderate atrophy. The bilateral postcentral areas, brainstem and cerebellum were spared.

Coronal sections of the fixed brain (Figure 3E–G) exhibited severe dilatation of the lateral ventricles and third ventricle and severe atrophy extending from the left temporal pole to the mesial part of the left parahippocampus, the left amygdala, and also the left insular cortex. Moreover, atrophy of the left hippocampus reached the outside of the subiculum. In contrast, the left transverse temporal gyrus was relatively well preserved. In the right hemisphere, the uncus, the anterior part of the superior temporal gyrus, and the parahippocampal gyrus were moderately atrophic. There were no abnormalities identified in the basal ganglia, thalamus, brainstem nuclei, or cerebellum.

Hematoxylin-eosin staining revealed neuronal loss, rarefaction of neuropils, and gliosis, mainly in the second and third layers of the cortex. The changes were prominent in the superior frontal gyrus, pars opercularis, insular cortex, inferior temporal gyrus, and parahippocampus of the left hemisphere (Figure 4). Although the amygdala showed rarefaction of neuropil and gliosis, other basal ganglia areas showed unremarkable findings. Pigmented cells in the locus coeruleus and substantia nigra were well preserved, and no Lewy bodies were identified. Neurofibrillary tangles and senile plaques were absent from the cortex, hippocampus, and brainstem. Argyrophilic neuronal inclusions (PBs) and ballooned neurons (Pick cells) (Figure 5) were observed in the limbic areas and the atrophic cerebral cortices (Figure 4). The pathological diagnosis was PiDPB.

DISCUSSION

The patient presented with a 6-year history of slowly progressive speech disturbance that began with AOS, marked by agrammatism and buccofacial apraxia, which was overlaid with bradykinesia, dysphagia, ideomotor, and ideational apraxia over the next 7 years. His general intelligence was
Figure 3. Macroscopic appearance and coronal sections of the brain. The left side of the brain is indicated by an L, and the right side by an R. Although the left frontal and temporal cortices exhibited generalized atrophy, the precentral gyrus, pars opercularis, superior temporal gyrus, temporal pole, and hippocampus in the left hemisphere demonstrated severe focal atrophy. In contrast, the parietal and occipital cortices were comparatively well preserved. The right-sided counterparts of the frontal and temporal lobes showed milder changes (E–G, anterior–posterior).
Figure 4. Distribution of cerebral cortical lesions. The lesions of neuronal loss, rarefaction of neuropils, and gliosis are classified into three categories: slight (hatched), moderate (sparsely cross-hatched), and severe (densely cross-hatched). A normal cerebral cortex is also shown (white). The black dots represent Pick bodies (PBs). The lesions where there are numerous dots demonstrate a high PB density. The left side of the brain is indicated by an L, and the right side by an R. The pars opercularis, precentral gyrus, temporal pole, insular cortex, and the limbic areas (amygdala and hippocampus) in the left hemisphere show severe cortical changes.

relatively well preserved for at least 10 years after disease onset, but it showed a progressive decline over the course of his illness. Atrophy was prominent in the pars opercularis, precentral gyrus, superior temporal gyrus, temporal pole, and the limbic areas in the dominant hemisphere. The pathological findings of this patient were consistent with those of PiD Type A (Constantinidis, Richard, & Tissot, 1974).

This patient was unique because of the specific combination of AOS as the initial symptom, detailed documentation of pathological findings correlating with his clinical features, and the detailed neuropsychological dataset that was recorded throughout the course of his illness. To the best of our knowledge, two other case reports and one case series are worth assessing with respect to the relationship between AOS as the initial symptom and the distribution of lesions (Broussolle et al., 1996; Fukui et al., 1996; Sakurai et al., 1998) (Tables 2.1, 2.2), and we have identified several clinicopathological similarities between our case and the Fukui et al. (1996) report.

Lesions responsible for AOS

Many studies have attempted to localize the brain lesions that contribute to AOS. Several case studies (Fox, Kasner, Chatterjee, & Chalela, 2001; Lecours et al., 1976; Mori, Yamadori, & Furumoto, 1989; Tonkonogy & Goodglass, 1981) have demonstrated that the inferior portion of the left precentral gyrus is responsible for AOS. Other studies reported by Dronkers (1996) suggest that AOS patients have lesions in the precentral gyrus of the insula. However, Hillis et al. (2004) have demonstrated that AOS is associated with structural damage or low blood flow in the left posterior inferior frontal gyrus. Josephs et al. (2006) suggest that the premotor and supplemental motor cortices are the main regions associated with AOS.

Because of these conflicting findings, we decided to review case reports with sufficiently detailed
Figure 5. Pathological findings of the cingulate gyrus and the amygdale of the dominant hemisphere. (A) Hematoxylin-eosin staining reveals many ballooned neurons (Pick cells) in the left cingulate gyrus. (B) Bodian staining shows many argyrophilic neuronal inclusions (Pick bodies) in the left amygdala.

The clinical and anatomical information (Tables 2.1, 2.2) to determine associations between patients identified with AOS and the distribution of lesions. We found that atrophy of the anterior operculum was demonstrated in all four documented cases, including ours, and atrophy of the left precentral gyrus in three of the four reviewed cases. On the basis of these findings, the following conclusion was made: AOS results from the anterior perisylvian cortical lesion (Ziegler, 2008), particularly the precentral gyrus and anterior operculum of the dominant hemisphere.

Moreover, we found similarities of pathological distribution between our case and that reported by Fukui et al. (1996). In both reports, focal atrophies were prominent in the left pars opercularis, lower precentral gyrus, frontal convexity, temporal pole, and superior temporal gyrus of the left hemisphere. Sakurai et al. (1998) reported a case where atrophy was restricted to the left precentral gyrus and frontal operculum, and neuronal loss was prominent in the pars opercularis, temporal tip, and anterior insula. In PiDPB marked with AOS, these areas may be causative lesions that lead to disease progression.

### Table 2.1
Summary of the clinical features of reviewed cases

| Case No. Author (published year) | Sex | Handedness | Age at onset/initial evaluation/initial sign | Other symptoms | Neuroimaging findings of initial assessment |
|----------------------------------|-----|------------|--------------------------------------------|----------------|--------------------------------------------|
| (1) this case                    | M   | right      | 56/62/69 AOS BFA                           |               | MRI: enlargement of the left Sylvian fissure and atrophy of the superior temporal gyrus, operculum, and insular cortex; SP: decreased uptake in the frontotemporal lobe and perisylvian area. |
| (2) Fukui et al., (1996)         | M   | right      | 62/66/70 AOS BFA, IMA, limb clumsiness    |               | MRI: moderate cortical atrophy in the left perisylvian region, paracentral gyrus, and superior parietal region; slight cortical atrophy in frontal convexity; left inferior horn enlargement, right > left hippocampus; SP: decreased uptake in the left perisylvian, paracentral, and upper parietal regions. |
| (3) Sakurai et al., (1998)       | M   | right      | 56/59/66 AOS None                          |               | CT: no abnormalities.                      |
| (4) Broussole et al., (case 6) (1996) | M   | NA         | 56/60/64 AOS BFA                           |               | CT: mild enlargement of frontal horns      |

*Note*: BFA, buccofacial apraxia; IMA, ideomotor apraxia; MRI, magnetic resonance imaging; CT, computed tomography; SP, SPECT (single-photon emission CT); NA, not available.
TABLE 2.2
Summary of pathological features of reviewed cases

| Case No. | Pathologic Dx BW (grams) (author, published year) | Atrophic center of macroscopic findings | Microscopic findings |
|----------|--------------------------------------------------|----------------------------------------|---------------------|
| (1) PiDPB 1068 (this case) | Left pars operculum, lower precentral gyrus, superior frontal gyrus, superior temporal gyrus, temporal pole, hippocampus, and amygdala | NL, RN, and gliosis, microvacuolation, spongiosis in 2nd-3rd layers prominent in pars operculum, temporal pole, insular cortex, superior frontal, inferior temporal, medial occipitotemporal gyrus, and parahippocampus in the left hemisphere. PBs in left frontotemporal lobe, hippocampus, amygdala, and basal ganglia. LB(-), NFT(-), SP(-). |
| (2) PiDPB * 1350 (Fukui, et al., 1996) | Left pars operculum and lower precentral gyrus | NL, RN, and gliosis in 2nd-3rd layers in lower posterior frontal lobe, insula, temporal pole, amygdala, and parahippocampus. PBs prominent in temporal lobe, hippocampus, parahippocampus, and posterior frontal lobe. LB(-), NFT(-), SP(-). |
| (3) PiDPB * 1120 (Sakurai, et al., 1998) | Left frontal operculum | NL, depletion of cortical layer structures, gliosis in frontal operculum, superior, middle frontal gyrus, lower premotor cortex and precentral gyrus. PBs in dentate, hippocampus, frontal, temporal, parietal, insular cortices, amygdale, putamen, and locus ceruleus. Neuronal achromasia and swollen neuritis in border zones between atrophied and intact cortices. Spongiosis (-). |
| (4) PFAS Not available (Broussole, et al., 1996) | Bilateral atrophy of precentral gyrus, anterior operculum, and inferior frontal gyrus | Nonspecific degenerative process and severe neuronal loss in all cortical layers, diffuse moderate astrocytosis, spongiform vacuolation in 2nd-3rd layers in bilateral precentral gyrus, anterior operculum, and inferior frontal gyrus. Rarefaction of Betz cells in bilateral lower precentral gyrus. SP(-), LB(-), NFT(-). |

Note: BW, brain weight, Dx, diagnosis; LB, Lewy bodies; NL, neuronal loss; NFT, neurofibrillary tangles; RN, rarefaction of neuropils; PB, Pick bodies; PiDPB, Pick’s disease with PB; PFAS, progressive focal atrophy syndrome; SP, senile plaques; * Left hemisphere was available for microscopic examination in No. 2 and 3.

Underlying pathological etiologies of AOS

Over the past few decades, there have been a series of published cases that have attempted to characterize the etiology of aphasia. Here, we reviewed a series of AOS case reports (Tables 2.1, 2.2). Of the three cases with pathological diagnoses of PiDPB, one exhibited progressive focal atrophy syndrome (Broussole et al., 1996; Fukui et al., 1996; Sakurai et al., 1998).

Josephs et al. (2006) reported that, of the seven cases reviewed in which AOS was the sole or dominant feature, five had a pathological diagnosis of PSP, one had a diagnosis of corticobasal degeneration (CBD), and one had a diagnosis of PiDPB. Furthermore, three progressive nonfluent aphasia (PNFA)–AOS cases, in which PNFA was more predominant than AOS, had CBD. The atypical distribution of the PSP pathology in these cases was more widespread, affecting cortical regions (Josephs et al., 2006).

Although PSP is reported to be the most predominant etiology, based on previous reports, PiDPB can account for more cases than PSP. Because AOS syndrome results from the damage of the perisylvian cortex and adjacent substructures, one may speculate that AOS syndrome is directly associated with PiDPB and atypical PSP/CBD.

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