

# Effect of Donepezil on Wernicke Aphasia After Bilateral Middle Cerebral Artery Infarction: Subtraction Analysis of Brain F-18 Fluorodeoxyglucose Positron Emission Tomographic Images

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**Abstract:** Aphasia is one of the most common neurologic deficits occurring after stroke. Although the speech-language therapy is a mainstream option for poststroke aphasia, pharmacotherapy is recently being tried to modulate different neurotransmitter systems. However, the efficacy of those treatments is still controversial. We present a case of a 53-year-old female patient with Wernicke aphasia, after the old infarction in the territory of left middle cerebral artery for 8 years and the recent infarction in the right middle cerebral artery for 4 months. On the initial evaluation, the Aphasia Quotient in Korean version of the Western Aphasia Battery was 25.6 of 100. Baseline brain F-18 fluorodeoxyglucose positron emission tomographic images demonstrated a decreased cerebral metabolism in the left temporoparietal area and right temporal lobe. Donepezil hydrochloride, a reversible acetylcholinesterase inhibitor, was orally administered 5 mg/d for 6 weeks after the initial evaluation and was increased to 10 mg/d for the following 6 weeks. After the donepezil treatment, the patient showed improvement in language function, scoring 51.0 of 100 on Aphasia Quotient. A subtraction analysis of the brain F-18 fluorodeoxyglucose positron emission tomographic images after donepezil medication demonstrated increased uptake in both middle temporal gyri, extended to the occipital area and the left cerebellum. Thus, we suggest that donepezil can be an effective therapeutic choice for the treatment of Wernicke aphasia.

**Key Words:** Wernicke aphasia, donepezil, F-18 FDG PET

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Aphasia is one of the most common neurologic deficits occurring after stroke. The prevalence of poststroke aphasia (PSA) is 21% to 38%, and there are considerable impacts of aphasia on the patients and their families.<sup>1</sup> Although speech-language therapy remains as the mainstream treatment for PSA, the effectiveness of conventional therapies has not been conclusively proven.<sup>2</sup> Recently, researchers have explored the effectiveness of pharmacotherapy, which modulates the neurotransmitters involved in language performance after stroke. However, the idea of using pharmacological agent to improve PSA is still controversial.<sup>1–4</sup>

Donepezil hydrochloride, a reversible acetylcholinesterase inhibitor, is in widespread use for Alzheimer disease. Berthier et al<sup>5,6</sup> found that the use of donepezil for 16 weeks significantly improved the severity of PSA. However, the effect of donepezil on

Wernicke aphasia after stroke is not clear yet. In this case, we present a patient with Wernicke aphasia after bilateral middle cerebral artery (MCA) infarction, who responded to donepezil treatment. Images were taken before and after the medication, by using a subtraction analysis of brain F-18 fluorodeoxyglucose positron emission tomographic (FDG PET).

## CASE REPORT

A 53-year-old, right-handed woman, who had experienced the left MCA infarction for 8 years, has undergone the recurrent right MCA infarction at 4 months before initially visiting (Fig. 1A). The patient's initial Aphasia Quotient of the Korean-Western Aphasia Battery (K-WAB) was 25.6 of 100 with the diagnosis of Wernicke aphasia (the score of fluency with 7.0, comprehension with 25.0, repetition with 2.0, and naming with 23.0) classified by Kertesz, and the initial score of the Korean Mini-Mental Status Examination (K-MMSE) was 16 of 30 (Table 1).<sup>7</sup> Baseline brain PET images demonstrated decreased cerebral metabolism in the left temporoparietal and right temporal area (Fig. 1B).

After the initial evaluation, 5 mg/d of donepezil was administered orally for 6 weeks and we increased the dosage to 10 mg/d for the following 6 weeks. Six weeks after the initial pharmacotherapy, the patient showed improvement in comprehension during a conversation and a slight increase of spontaneous speech. Three months after donepezil treatment, the patient's K-WAB and K-MMSE scores improved to 51.0 and 21, respectively (Table 1). The family members of the patient gave informed consent. All procedures were performed with the approval of the Institutional Review Board for Clinical Studies.

## ACQUISITION AND SUBTRACTION ANALYSIS OF F-18 FDG PET IMAGES

Brain F-18 FDG PET scan using a GE Advanced PET scanner (GE, Milwaukee, WI) was performed before the initial administration of donepezil and at the follow-up after 3 months of treatment with donepezil. Subtraction analysis of brain PET images of before and after donepezil medication was performed by a SISCOM analysis (SISCOM, Dayton, OH) implemented in SPM99 software (Wellcome Department of Cognitive Neurology, London, England). Then, the subtracted image was superimposed on a standard T1-weighted magnetic resonance imaging (MRI), and 20% of increase in brain metabolism was considered to be significant. Co-registration of the subtracted PET image and the patient's MRI was performed using Analyze 9.0 software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN). The transformed, normalized baseline image was subtracted from the follow-up image. The resulting subtraction image was set to display only voxels with values greater than 2 standard deviations above the mean, and those voxels were co-registered to the patient's MRI.<sup>8</sup> The results of anatomical localization using co-registered image of the subtracted PET image and the patient's

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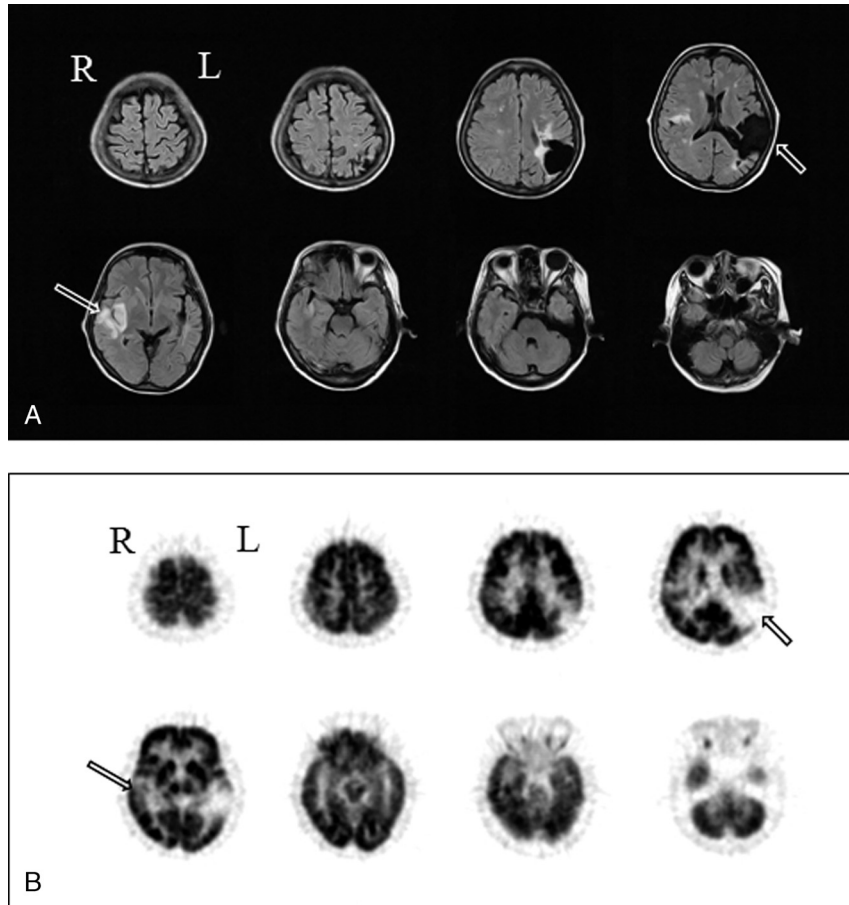
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**FIGURE 1.** A, Bilateral MCA infarction as shown in initial brain T2 flair MRI. B, The F-18 FDG PET image showing decreased cerebral metabolism in the left temporoparietal and the right temporal cortices.

MRI revealed significantly increased F-18 FDG uptake in both middle temporal gyri, extended to the occipital area and the left cerebellum (Fig. 2).

**DISCUSSION**

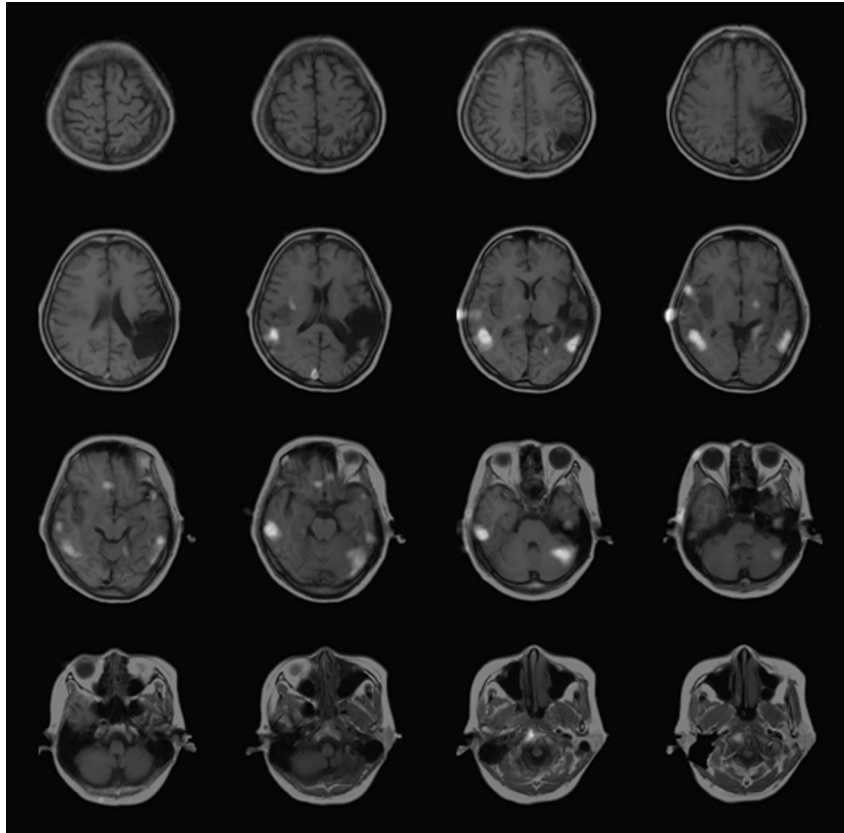
Pharmacological intervention for PSA has been tried with the noradrenergics, dopaminergics, cholinergics, and glutamaterics. However, the effectiveness of pharmacotherapy in the improvement of language function is still controversial.<sup>1-4</sup> Among those treatments, a few reports that modulated the cholinergic system for PSA postulated that the enhancement of cholinergic function might improve lexical-semantic processes and verbal memory. Thus, acetylcholine-enhancing agents might be used to improve the comprehensive ability after temporal lobe injury.<sup>4</sup> In our case, 3 months of donepezil administration for Wernicke aphasia improved K-WAB and K-MMSE scores and significantly increased F-18 FDG uptake in both middle temporal gyri and the left cerebellum.

Cholinergic stimulation has a direct effect on cerebral vessels, thus acetylcholine pathways are vulnerable to vascular damage.<sup>9</sup> Because neuronal activity is tightly coupled to vascular brain perfusion, it seems possible that the beneficial effect of donepezil may be attributed to the improvement of neurovascular coupling.<sup>9</sup> Previous studies reported that donepezil treatment for patients with cognitive impairment increased cerebral blood flow on the temporal areas, which is in accordance with our findings.<sup>10-12</sup>

Our case can propose that donepezil might restore the brain function by promoting a reorganization of perilesional cortical networks and a better control of regional cerebral blood flow in both temporal areas, which consequently enhanced the language and cognition functions in bilateral MCA infarction.<sup>5,6,9</sup> Another possible mechanism of donepezil ameliorating language deficit in this case can be suggested by the enhancement of sensory input processing by augmenting temporal lobe function.<sup>13</sup> Also, the recovery of general cognition after medication may contribute to the language performance improvement.

**TABLE 1.** The Changes in the K-WAB and the K-MMSE, Before and After Donepezil Medication

		Before Medication	After Medication
K-WAB	Spontaneous speech	9	15
	Comprehension	25	109
	Repetition	2	4
	Naming	23	46
	Aphasia Quotients	25.6	51.0
K-MMSE		16	21



**FIGURE 2.** The co-registered image of the subtracted PET image and the patient's MRI image, revealing that both middle temporal gyri extended to the occipital area and the left cerebellum exhibited increased brain metabolism after the administration of donepezil.

Furthermore, our finding that donepezil treatment increased cerebellar metabolism can be interpreted by the recovery of crossed cerebellar diaschisis. Crossed cerebellar diaschisis means a decreased metabolism and blood flow in the contralateral cerebellar hemispheres to a remote supratentorial lesion. The interruption of afferent corticopontocerebellar pathways causes a remote functional cerebellar depression by a reduced excitatory input.<sup>14–16</sup> Crossed cerebellar diaschisis is reversible functional inactivation, thus recovery of supratentorial lesion with contralateral cerebellum could be possible. In our case, increased metabolism in the left cerebellum might have arisen from the metabolic recovery in the perilesional area of the right temporal lobe infarction after medication. However, there is a limitation because the left cerebellar involvement of the visuospatial organization in language performance has not been evaluated in our case.<sup>17</sup> Thus, further study evaluating the visuospatial function is recommended.

Our study indicates that donepezil can be an effective therapeutic choice for the improvement of language performance in patients with Wernicke aphasia. Further controlled research with large samples is needed to confirm the efficacy of donepezil in Wernicke aphasic patients.

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