IV. 1. Raclopride and FDG PET Findings in Two Patients with Alzheimer's Disease with Behavioral and Psychological Symptoms of Dementia

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Introduction
Since the behavioral and psychological symptom of dementia (BPSD) such as wandering is a burden for family and caregivers, the neurobiological mechanism should be clarified. Using positron emission tomography (PET), we previously reported that wandering behavior in dementia was associated with decreased front-temporal glucose utilization and impaired striatal dopamine metabolism (decreased dopa uptake and increased D2 receptor density)\(^1\).

Here, we investigated the relationship between the severity of BPSD and change of the striatal D\(_2\) receptor in Alzheimer's disease (AD).

The tracers used were \([^{11}C]\) raclopride (D\(_2\) antagonist) and the \([^{18}F]\) FDG. The uptake of \([^{11}C]\) raclopride was calculated as the binding potential (BP)\(^2\) of the striatum to the cerebellum. Regional glucose utilization was measured according to the autoradiographic method\(^3\). We evaluated their BPSD status by the BEHAVE-AD-FW scale\(^4\).

Method

Subjects
Two patients with probable AD with moderate severity of dementia as per the NINCDS-ADRDA criteria\(^5\) were studied. Neither patient showed visual symptoms, or extrapyramidal signs such as rigidity, and neither met the criteria for the clinical diagnosis of probable or possible dementia with Lewy bodies (DLB)\(^6\).

The Medical Ethics Committee of the Cyclotron Radioisotope Center at Tohoku
University approved this study, and informed consent was obtained from all the subjects and their families.

**Behavioral observations**

The behavioral pathology in Alzheimer's disease rating scale referred to as the Behave-AD was specifically designed to assess BPSD that would be remediable to both psychologic and pharmacologic intervention\(^7\). We used this scale with frequency-weighted version.

**\(^{18}F\) FDG PET**

The PET study was performed with a model PT-931 scanner (CTI Ind., USA: axial/transaxial resolutions; 6 mm), according to the \(^{18}F\)-fluoro-deoxyglucose (FDG) method\(^3\). The procedure and the analysis for rCMRglc was the same as in previous study\(^8\). A total of 5 regions of interest (ROIs), round, 2.7 cm\(^2\), in each hemisphere were placed manually. The rCMRglc values in the following bilateral regions were measured: bilateral upper frontal, temporal, parietal, temporoparieto-occipital (TPO), and hippocampus.

**\(^{11}C\) Raclopride PET**

The binding potential (BP) of D\(_2\) receptors was assessed using a SET-2400 (Shimazu Ind.) camera and \(^{11}C\) raclopride as a radioligand. Scans were performed using 4-11 mCi of \(^{11}C\)-raclopride (1279-10438 Ci/mmol) following a bolus plus infusion protocol. PET data were acquired 40 to 70 minutes after injection, and data were corrected for decay and attenuation. Regions of interest (ROIs) were drawn on three adjacent slices for both the left and the right striatum (caudate and putamen), and for the cerebellum. The ratio of counts in the striatum and cerebellum (Eq. 1), during the period of pseudoequilibrium is used as an estimate of the Bmax/Kd of \(^{11}C\) raclopride for dopamine D\(_2\) receptors\(^9\). This is justified on the grounds that the cerebellar (C) counts reflect non-specific binding and free ligand, whereas the striatal (S) counts reflect specific binding of the ligand to D\(_2\) receptors in addition to the non-specific and free ligand binding. Using these assumptions, it can be shown that the (S-C)/C ratio reflects the ratio of Bmax/Kd, where Bmax is the total number of D\(_2\) receptors and Kd is the affinity of the ligand\(^{10,11}\). This measure is often referred to as the BP.
D$_2$ binding potential = $\frac{(S - C)}{C}$  \hspace{1cm} (1)

S: counts in the striatum, C: counts in the cerebellum.

**Case Reports**

*Case A.A*

A 68-year-old, female is in a nursing home since December 18, 2000. BEHAVE-AD-FW score was 17, and symptoms were mildly troubling to the caregiver. Her background history is uninformative on education. Her previous occupation included farmer, janitor of a school, and caregiver for elderly persons. Her previous medical history included bilateral femoral neck fractures, glucose intolerance, and transient ischemic thrombosis at the age of 46. She has not suffered from any mental disorder or manifested any psychotic symptoms earlier in life. In 1999, diurnal rhythm disturbance and inappropriate behaviors, especially inappropriate exposure started to appear. These symptoms worsened, and she was admitted to the specialized unit for dementia.

Neurological examination revealed no particular findings, there were no extra-pyramidal signs, increased tone or other features of motor dysfunction. Neuropsychological assessment performed on September 2001, revealed cognitive decline. MMSE score was 4, and she obtained zero scale on Wechsler Adult Intelligence Scale-Revised, and she showed dressing apraxia. No clinical symptoms of depression were present.

Brain magnetic resonance imaging (MRI) revealed atrophy of the fronto-temporal cortices and hippocampus, with no evidence of ischemic lesions (Fig. 1).

*Case S.K*

SK is an 81-year-old woman with ten years of formal education. Her previous medical history includes hypertension only. She had been in good physical and mental health till 1994. According to her family, inappropriate behavior, especially aggression and inattention to personal hygiene, has been seen from the period. Since her husband was admitted in 2000, she changed her residence and lived together with her son's family. She attended adult day-care four times a week since June 2000, and her BEHAVE-AD-FW score was 18. Behavioral symptoms were severely troubling to the families.

She was referred to the Rehabilitation Department of Tohoku University Hospital, for evaluation and treatment of dementia. In January 2002, SK underwent a full neuropsychological examination, showing a mildly poor cognitive profile, with short time
memory deficit, and frontal executive function disorder. MRI showed no evident cortical atrophy (Fig. 2). Electroencephalogram, single photon emission computed tomography (SPECT) with [123I] IMP and the FDG-PET study revealed frontal dysfunction.

**Functional imaging study**

Both patients underwent the raclopride and the FDG-PET studies. FDG-PET showed low metabolic activity of the bilateral fronto-temporal area in both patients (Fig. 3). And BP was 1.99 for right and 2.15 for left in SK, 1.71 for right and 1.89 for left in AA (Fig. 4,5).

**Comments**

Previous finding of decreased frontal glucose metabolism in BPSD patients was confirmed. The previous report 1) using the [11C] YM09151-2, reported that wandering behavior in AD was correlated with increased levels of D2 receptors. In this study we did not compare with the profiles of healthy controls, thus further research is needed in this point.

Recent PET studies in dopaminergic system reported that the striatal reuptake of dopamine was reduced with reference to extrapyramidal symptoms12) and with regional CMRglc (Meguro et al. 1997). Another report 13) said that there was no reduction in the uptake of [11C] raclopride in the caudate nucleus of relatively early stage of AD. Provided we could compare the profiles with age and sex matched healthy controls in future study, we could mention that there would be a functional neural network or "loop" between the striatum and the fronto-temporal lobe. This network between the frontal cortex and striatum may relate with abnormal behavior in AD.

**References**


Fig. 1. AA's MRI (TR400, TE12) there is no remarkable infarction, and is cortical atrophy.
Fig. 2. SK's MRI (TR440, TE11) the cortical atrophy is mild, ventricle enlargement can be observed.

Fig. 3. FDG-PET, AA: left, frontal and parietal hypo-metabolism was seen, SK: right, frontal hypo-metabolism was seen.

Fig. 4. Raclopride-PET, AA: left, SK: right. Symmetrical uptake was observed in striatal area for both patients.
Fig. 5. Binding Potential and BEHAVE-AD-FW, no correlation can be seen in this data.