We herein investigated the dopaminergic neuronal function of the parkinsonism, responsive to levodopa therapy, in a type 3 Gaucher disease patient and his father using positron emission tomography (PET) and thus showed that our cases were involved in presynaptic dopaminergic function seen in Parkinson's disease.

## 2. Clinical reports

A 38-year-old Japanese man complained of difficulty in walking and a reduced speed in the normal activities of daily life. He was found to have hepatosplenomegaly at the age 6. A bone marrow analysis revealed a marked accumulation of Gaucher's cells and his glucocerebrosidase activity level was 1.8 nmol/h/mg protein (control level; 4.1–9.6 nmol/h/mg protein). He developed a generalized tonic–clonic seizure with abnormal electroencephalogram patterns at age 7 and thus was treated with anti-convulsant therapy. A neurological examination at the age 7 slowed horizontal saccadic eye movements characteristic of type 3 Gaucher disease. He was diagnosed to have type 3 Gaucher disease and thus underwent a splenectomy in early adolescence. He also suffered from spinal bone pain and abdominal pain associated with hepatomegaly at the age 28. After the initiation of enzyme replacement therapy at the age 33, the hepatomegaly and the bone pain both were improved, however, the patient gradually developed a clumsy left hand, start hesitation and freezing of gait during turning. He was unable to walk without assistance by the age 37 and thereafter presented at our hospital. His family history revealed no consanguinity and no history of Gaucher disease. A neurological examination revealed that he showed severe akinesia with a tendency to show trunk deviation to the left in the sitting position and he was unable to get up from a chair without help. He walked with a flexed posture, with small and irregular steps, while demonstrating start and turn hesitation and a reduction in his arm swing. Slurred speech, hypophonia, micrographia and generalized rigidity were also observed, as well as slowed horizontal saccadic eye movements. All other neurological examinations were unremarkable; in particular involuntary movement including tremors, and muscle strength, stretch and cutaneous plantar reflexes, co-ordination, sensory functions, or fundi and other cranial nerves were normal. A mental examination showed him to be inert. Spatial abilities were intact. His digit span was six forward, and four backward. He could repeat a seven-item name and address immediately after its oral presentation and could recall 6 of 7 items after a 5-minute delay. The Wechsler Adult Intelligence Scale (WAIS) showed verbal IQ of 60, performance IQ of 53, and full scale IQ of 52His Mini Mental State Examination (MMSE) score was 26. An electroencephalogram showed some sharp waves or spike and wave complexes over both parietal-occipital regions and abundant generalized discharges of spikes, polyspikes and slow wave complexes. Magnetic resonance imaging showed no abnormality in the brain. A slit-lamp examination and laboratory studies including thyroid function tests, serum copper and ceruloplasmin were all normal. The study of an auditory brainstem response in this patient showed no deterioration.

His 71-year-old father presented to our hospital in order to help his son. He also became aware of progressive difficulty of slowness during walking and developed a left clumsy hand at the age of 63. A neurological examination showed bradykinesia, symmetrical cogwheel rigidity of the upper limbs and poor backward postural reflexes. His sense of touch, vibration, position and cognitive abilities were intact. Her 65-year-old mother was asymptomatic. A neurological examination was unremarkable.

After PET studies of the proband and his farther, anti-Parkinson therapies including levodopa/carbidopa, cabergoline and selegeline HCl were initiated. The parkinsonian features in both patients showed a favorable response to the medication. The patient was able to walk without assistance and showed an improvement in both akinesia and rigidity. The Unified Parkinson disease rating scale (UPDRS) III motor score in the proband improved from 45 to 28. His father also improved from 23 to 16. During the follow-up, the proband showed a gradual appearance of a wearing-off phenomenon, motor fluctuations and levodopa-induced dyskinesia.

## 3. Methods and results

### *3.1. Molecular genetic analysis*

Genomic DNA samples isolated from blood samples were subjected to restriction fragment length polymorphism (RFLP) analyses to identify any mutations in the glucocerebrosidase gene by a previous described method [9] For a molecular genetic analysis for hereditary Parkinson disease, the sequencing of the gene for α-synuclein and parkin was performed by a previously reported technique [10,11]. The genetic study demonstrated that the proband carried two known missence mutations in the glucocerebrosidase gene, L444P in exon 10 and F213I in exon 6 (Fig. 1A). The RFLP analyses of his father demonstrated a L444P mutation on the paternal allele. No mutations in the α-synuclein gene or the parkin gene were identified in the proband and his father.

### *3.2. PET scan*

PET was performed by a high-resolution brain PET scanner (SHR12000, Hamamatsu Photonics K.K., Hamamatsu, Japan). The head of a patient was fixated using a thermoplastic face-mask enabling to fix it to the same place between separate PET measurements. First, 72 min after a bolus intravenous injection of the [$^{11}$C] CFT, 20-minute PET data were collected to produce a late-phase image of [$^{11}$C] CFT uptake [12]. Next, following three hours to allow for a decay of [$^{11}$C] CFT radioactivity, the same patient were scanned for 62 min after [$^{11}$C] raclopride injection using a

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serial scans protocol [13] The final PET images were generated as semi-quantitative parametric images (a standardized uptake value image for [$^{11}$C] CFT, and a distribution image for [$^{11}$C] raclopride). Based on the regions of interest (ROIs) method, we placed the ROIs on the caudate nucleus, putamen and cerebellum on the MR images, and then transferred them onto the corresponding PET images, and finally calculated a semi-quantitative striatum/cerebellum ratio by dividing the ROI counts of either the caudate nucleus or the putamen by cerebellar counterparts. The ratio from a patient and his father was compared with the ratios from three normal control subjects and assessed statistically

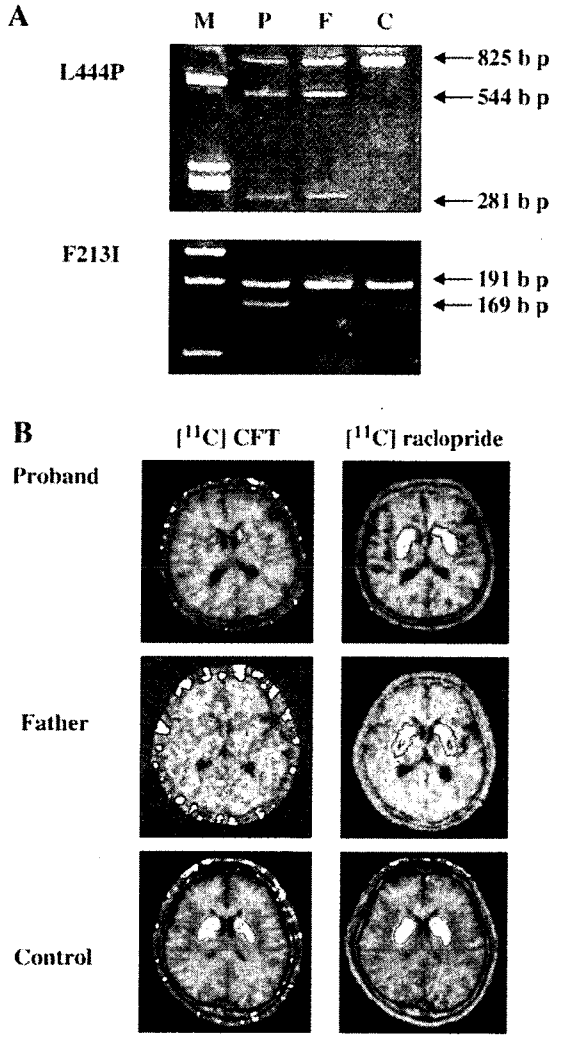


Fig. 1. A. Restriction fragment length polymorphism analyses of the L444P and the F213I mutation in the patient and his father. When the L444P mutation is present, restriction enzyme (NciI) digests an 825 bp PCR product, thus producing two fragments of 544 bp and 281 bp. When the F213I mutation is present, a restriction enzyme (AseI) digests a 191 bp PCR thereby producing two fragments of 169 bp and 22 bp M: molecular marker, P: patient, F: patient's father, C: control. B. Transaxial PET slices blended with MRI images of the proband, his father and a 38-year-old healthy man as a control.

Table 1

| | Patient | His father | Normal subjects ($n$=3) (mean±S.D.) |
|---|---|---|---|
| [$^{11}$C] CFT | | | |
| Caudate nucleus/cerebellum ratio | 1.82 | 1.56 | 3.83±0.07 |
| Putamen/cerebellum ratio | 1.42 | 1.37 | 3.90±0.13 |
| [$^{11}$C] raclopride | | | |
| Caudate nucleus/cerebellum ratio | 3.93 | 3.72 | 4.33±0.13 |
| Putamen/cerebellum ratio | 4.02 | 4.14 | 4.49±0.31 |

The uptake of [$^{11}$C] CFT in the both putamen and caudate nucleus was significantly reduced at $p<0.05$ by one sample $t$-test.

by one sample $t$-test (Table 1). The PET images of the patient and his father showed similar results. The uptake of [$^{11}$C] CFT in the both putamen and caudate nucleus was significantly reduced ($p<0.05$), while the [$^{11}$C] raclopride uptake showed a relative decrease in the same striatal regions in comparison with normal counterparts.

## 4. Discussion

This report documented fascinating clinical and PET findings in two patients with the same family lineage who both developed parkinsonism. The clinical features of our cases are as follows; 1) the proband with type 3 Gaucher disease and his father developed parkinsonism, 2) molecular genetic analyses in the glucocerebrosidase gene showed the proband to be compound heterozygous for L444P and F213I, while his father is heterozygous for the L444P mutation, 3) the parkinsonism showed a favorable response to anti-Parkinson therapies and 4) a dopaminergic functional neuroimaging study of both patients showed a presynaptic dopaminergic dysfunction which is normally seen in Parkinson's disease patients. Parkinsonism has been described as a rare neurological phenotype of patients with type 1 Gaucher disease [2,3] The parkinsonism in such patients is characteristically early-onset and most tend to show a poor response to levodopa therapy. The enzyme replacement therapy is not effective for the treatment of the parkinsonism in such cases. The neuropathological findings characteristic to Gaucher disease with parkinsonism showed a marked loss of dopaminergic neurons in the substantia nigra, synuclein-positive Lewy bodies and the involvement of hippocampal CA2-4 regions where glucocerebrosidase was expressed [5,14]. While the concurrence of Gaucher disease and parkinsonism could still be coincidental, the shared clinical characteristics and neuropathology of previous case reports suggest a related etiology. In our proband the diagnosis of Gaucher disease was firmly established both by a deficiency in the glucocerebrosidase activity and the gene analysis in the glucocerebrosidase gene. The first clinical manifestations including hepatosplenomegaly, slow saccadic eye movements and epilepsy preceded by osseous pain, appearing in adulthood, suggest our case to have type 3 Gaucher disease The L444P and the F213I mutations identified in our patients

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are frequent in patients affected with both type 1 and 2 as well as type 3 Gaucher disease [1,9]. Although the correlation between genotypes and phenotypes in Gaucher disease is investigated, the conclusion remains elusive [1] Although many reports have demonstrated a clinical association between type 1 Gaucher disease and parkinsonism, type 3 Gaucher disease with parkinsonism is uncommon. The proband appeared to have early-onset parkinsonism which developed in his 30's as previous reports in type 1 Gaucher disease patients with parkinsonism [5]. The patient's father who carried the L444P allele developed parkinsonism in his 60's. A recent study demonstrates that parkinsonism appears to be associated with heterozygosity for a mutation in the glucocerebrosidase gene [8]. This observation indicates that the L444P mutation found in the father, even in heterozygotes, may thus be a risk factor for the development of parkinsonism. The correlation between parkinsonism as a phenotype and mutations in the glucocerebrosidase gene as a genotype has not yet been established. N370S, L444P, 84GG mutations are reported as common mutations associated with parkinsonism in Gaucher disease patients and their carriers, however, it is evident that the majority of the patients or carriers with such mutations do not always develop parkinsonism [4,5,8] An intriguing clinical feature of our patients was the fact that they had treatment-responsive parkinsonism, because initial case reports showed the parkinsonian symptoms in Gaucher disease patients to be refractory to levodopa therapy [2,3,5]. In addition, the association between a favorable response to L-Dopa and the mutation in patients with Gaucher disease has been reported in some studies. Bembi et al. reported 4 cases with a good response to L-Dopa who had either N370S, L444P or G337S mutation [4]. Goker-Alpan et al. also showed some cases with a good response to L-Dopa therapy and they had either N370S or L444P mutations, however, not all the patients with such a mutation always showed an effective response to L-Dopa therapy [8].

We evaluated the dopaminergic function of our patients using neuroimaging techniques with a PET system [$^{11}$C] CFT, a dopamine transporter probe, allows us to study the integrity of the presynaptic dopaminergic system [12]. [$^{11}$C] raclopride, a low affinity dopaminergic D2 receptor ligand, has been used to study the post synaptic dopaminergic function [13]. The PET study with the combined use of [$^{11}$C] CFT and [$^{11}$C] raclopride in our patients who both carried the L444P mutation allele showed a presynaptic dopaminergic dysfunction The mutation in the glucocerebrosidase gene, even in heterozygosis, may be associated with the presynaptic dopaminergic neuronal dysfunction which shares a common pathogenesis to Parkinson's disease. It is not clear why the parkinsonism associated with mutations in the glucocerebrosidase gene shows such variation in the responsiveness to levodopa therapy. We speculate that at the onset of the parkinsonism, this mutation may be associated with a dysfunction of presynaptic dopaminergic neuron and then, during the progression of the parkinsonism, the patient may develop dysfunction of postsynaptic dopaminergic neurons resulting in the poor responsiveness to levodopa therapy. Another possibility may be that other genetic or environmental factors may interact with the glucocerebrosidase gene thus resulting in the development of variation in the responsiveness to anti-Parkinson therapy. It is important to be aware of the association between Gaucher disease and parkinsonism. We should therefore investigate parkinsonian symptoms in not only probands of Gaucher disease but also their family members. A PET study to evaluate pre- and postsynaptic dopaminergic neuronal function provides an excellent understanding of an association with Gaucher disease and Parkinson's disease.

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# *In vivo* presynaptic and postsynaptic striatal dopamine functions in idiopathic normal pressure hydrocephalus

Yasuomi Ouchi[1], Teiji Nakayama[2], Toshihiko Kanno[1], Etsuji Yoshikawa[3], Tomomi Shinke[3] and Tatsuo Torizuka[1]

[1]*Positron Medical Center, Hamamatsu Medical Center, Hamamatsu, Japan;* [2]*Department of neurosurgery, Hamamatsu Medical Center, Hamamatsu, Japan;* [3]*Central Research Laboratory, Hamamatsu Photonics KK, Hamamatsu, Japan*

**Differentiation of impaired gait seen in idiopathic normal pressure hydrocephalus (iNPH) from parkinsonian gait is sometimes a great challenge and important for future medication in the clinical setting. To investigate dopaminergic contribution to its pathophysiology, two aspects of the transsynaptic dopamine functions in the striatal region in eight iNPH patients naïve to dopaminergic drugs were examined using positron emission tomography with a presynaptic marker [$^{11}$C]CFT ([$^{11}$C]2-$\beta$-carbomethoxy-3$\beta$-(4-fluorophenyl) tropane) that binds to dopamine transporter and a postsynaptic marker [$^{11}$C]raclopride that binds to D2 receptor. Quantitative values of binding potentials (BPs) for [$^{11}$C]CFT and [$^{11}$C]raclopride were compared between patients and eight age-matched healthy subjects. The BPs and magnetic resonance imaging-based morphometric measures in iNPH were used for correlation analyses between the magnitude of binding of these *in vivo* markers and clinical severity of the patients. Analysis of variance showed significant reduction in [$^{11}$C]raclopride binding in the putamen and nucleus accumbens ($P<0.05$, corrected for multiple comparison) and unchanged striatal [$^{11}$C]CFT binding in iNPH. The dorsal putamen [$^{11}$C]raclopride binding correlated negatively with gait severity ($r=0.720$, $P<0.05$), and the nucleus accumbens [$^{11}$C]raclopride binding correlated positively with emotional recognition score ($r=0.727$, $P<0.05$) in the disease group. No significant relationship was observed between BPs and morphometric measures. The current result of the postsynaptic D2 receptor reduction along with preserved presynaptic activity in the nigrostriatal dopaminergic system reflects a pathophysiology of iNPH. Postsynaptic D2 receptor hypoactivity in the dorsal putamen may predict the severity of gait impairment in iNPH.**
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**Keywords:** CFT; idiopathic normal pressure hydrocephalus; positron emission tomography; raclopride; striatum

## Introduction

Clinical features of normal pressure hydrocephalus (NPH) are gait disturbance, progressive dementia, and urinary incontinence, known as a clinical triad (Hakim and Adams, 1965). The NPH symptoms are thought to be a clinical entity that can be treated by surgical interventions such as shunting (Adams *et al*, 1965). The possible treatment of this disease led us to explore a surrogate marker for NPH that enables proper diagnosis at an early stage. Clinically, gait disturbance is likely the first sign and important symptom in NPH (Fisher, 1982). However, the hypokinetic type of gait disturbance is often seen in other neurologic diseases such as Parkinson's disease (PD) and dementia with extrapyramidal symptoms. Differentiating NPH from PD may be possible by observing improvement of gait velocity after withdrawal of cerebral spinal fluid (CSF) (Sudarsky and Simon, 1987) or after L-dopa treatment (Blin *et al*, 1991). However, one difficulty is that some NPH patients suffer from parkinsonism that can be ameliorated by surgical shunt (Curran and Lang, 1994). A recent case report with positron emission tomography (PET) on noncommunicating

Correspondence: Dr Y Ouchi, Positron Medical Center, Hamamatsu Medical Center, 5000 Hirakuchi, Hamamatsu 434-0041, Japan.
E-mail: ouchi@pmc.hmedc.or.jp
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NPH patient (acqueductal stenosis) with parkinsonism showed reduction in [$^{18}$F]Dopa uptake in the basal ganglia, suggesting involvement of dopaminergic derangement in patients with NPH (Racette *et al*, 2004). Morphological investigations on the midbrain in secondary NPH patients favor a mechanical theory that accounts for developing parkinsonism in NPH (Jankovic *et al*, 1986; Zeidler *et al*, 1998). However, there have been no reports about the dopaminergic alterations in patients with idiopathic, communicating NPH.

Combination of a presynaptic dopamine transporter radiotracer, [$^{11}$C]2-$\beta$-carbomethoxy-3$\beta$-(4-fluorophenyl) tropane ([$^{11}$C]CFT), and a predominantly postsynaptic D2 receptor radiotracer, [$^{11}$C]raclopride, in PET studies allows us to evaluate presynaptic and postsynaptic dopaminergic activities in the basal ganglia (Farde *et al*, 1986; Ouchi *et al*, 1999*a*). The *in vivo* findings characteristic of early PD were an asymmetric pattern of tracer binding, that is, decreased binding of presynaptic radiotracer and normal or increased binding of postsynaptic radiotracer (Ouchi *et al*, 1999*a*), and differences in regional susceptibility (Ouchi *et al*, 1999*b*) in line with the pathologic finding (Fearnley and Lees, 1991; Kish *et al*, 1988). Likewise, it can be speculated that there will be an uneven pattern of tracers' accumulation in the dopaminergic projection areas in idiopathic communicating NPH, because morphological change of the midbrain might be related to severity of gait impairment in the disease (Lee *et al*, 2005).

The purpose of this study was to measure quantitatively the binding potentials (BPs) of [$^{11}$C]CFT and [$^{11}$C]raclopride in drug-naive patients with idiopathic normal pressure hydrocephalus (iNPH) on the same day, because any delay in the measurement of the two tracers could devalue the accurate relationship of the viability of presynaptic and postsynaptic dopaminergic neurons that might be affected by increased intraparenchymal fluid of CSF (Owler *et al*, 2004) in the living brain.

## Materials and methods

### Subjects

Eight patients with iNPH who were all naïve to dopaminergic drugs (five men, three women: mean age 72.4 years $\pm$4.0 s.d. (range 64 to 77)), and eight age-matched healthy subjects (six men, two women, mean age 66.9 years $\pm$ 4.5 s.d. (range 62 to 73)) participated in the current study. Diagnosis of iNPH was based on the clinical and imaging features: gait disturbance, cognitive deterioration with more or less urinary incontinence, normal lumber CSF pressure $<$20 cm $H_2O$ (Adams *et al*, 1965; Hakim and Adams, 1965), and enlargement of the brain ventricles with some degree of deep white matter hyperintensities and reduction of the cortical sulcal space in the superior convexity on the coronal view of magnetic resonance imaging (MRI) (Kitagaki *et al*, 1998). The morphological MRI and neurologic and blood tests excluded a possibility of secondary NPH and other neurologic diseases such as progressive supranuclear palsy or corticobasal degeneration. In the present study, however, half of the patients were on medication for internal diseases (Table 1). Patient No. 3 had a small meningioma in the cerebellum, which was considered irrelevant to the NPH etiology. As shown in Table 1, no patients suffered from extrapyramidal symptoms such as rigidity or tremor but freezing, magnetic gait, cognitive decline, and some degree of difficulty in urination were observed. A CSF tap test (Wikkelso *et al*, 1986) after PET measurement was performed to support the diagnosis and introduction of shunt surgery. All medicines for their accompanying diseases were temporarily ceased 12 h before the PET measurement. All subjects were free from regular use of neuroleptic and hypnotic drugs. The current study was approved by the local Ethics Committee of the Hamamatsu Medical Center, and written informed consent was obtained from all participants after full explanation of the nature of the present study.

### Psychological and Behavioral Assessments

The tests consisted of a general cognition and memory test (Mini-Mental State Examination: full score = 30); an affect

**Table 1** Clinical characteristics of idiopathic normal pressure hydrocephalus patients

| *No.* | *Age* | *Sex* | *DD* | *MMSE* | *Gait* | *UI* | *Complications* | *T2-MRI* | *Medication* | *AT* | *NT* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 71 | F | 3.0 | 25 | 1 | 2 | None | VD | None | 15 | 18.3 |
| 2 | 77 | F | 1.2 | 14 | 2 | 3 | None | sWM HIAs, VD | Anti-pollakiuria | 6 | 21.0 |
| 3 | 76 | F | 1.1 | 24 | 1 | 2 | None | VD, Cer tumor | None | 8 | 13.0 |
| 4 | 71 | M | 0.5 | 23 | 1 | 3 | HT, Arrhythmia | sWM & BG HIAs, VD | Anti-HT | 16 | 14.8 |
| 5 | 74 | M | 4.0 | 23 | 2 | 2 | None | VD | None | 15 | 16.2 |
| 6 | 74 | M | 6.0 | 25 | 2 | 3 | HT | sWM HIAs, VD | Anti-HT | 15 | 14.5 |
| 7 | 72 | M | 1.1 | 26 | 1 | 3 | HT | sWM HIAs, VD | Anti-HT | 18 | 12.6 |
| 8 | 64 | M | 1.0 | 27 | 1 | 1 | None | VD | None | 20 | 13.5 |

DD: disease duration from onset to PET measurement (year); MMSE: mini-mental state examination; Gait: 0 = normal, 1 = insecure, 2 = insecure with any support, 3 = wheelchair; UI: urinary incontinence (0 = none, 1 = present without a diaper on, 2 = present occasionally with a diaper on, 2 = diaper requisite); VD: ventricular dilatation; sWM: subcortical white matter; HIAs: high intensity areas; BG: basal ganglia; Cer: cerebellum; SAH: subarachnoid hemorrhage; HT: hypertension; anti-HT: anti-hypertensive drug; AT: affect test with the full score of 20; NT: navigation time (second).

test in which subjects evaluate facial expressions on different cards by choosing appropriate answers from the following basic affects: happiness, sadness, surprise, disgust, anger, fear (full score = 20), and a walking test (the time required for navigating a 5-m-long path on a flat corridor both ways). Our preliminary examination showed that 11 healthy subjects (mean age = 50.4 years) scored more than 28 on the MMSE, 20 in the affect test, and took < 10 secs in the back-and-forth walk (data not shown).

### Magnetic Resonance Imaging and Positron Emission Tomography Procedures

We performed three-dimensional MRI for all participants just before the PET measurement using a static magnet (0.3 T MRP7000AD, Hitachi, Tokyo, Japan) with three-dimensional mode sampling to determine the areas of the midbrain and the striatal nuclei for setting the regions of interest (ROIs) and ventricles for morphometric analysis. The MRI measures and a mobile PET gantry allowed us to generate PET images parallel to the intercommisural (ACPC) line without reslicing during image reconstruction; using this approach, we were able to allocate ROIs on the target regions of original PET images (Ouchi *et al*, 1999*b*).

For PET scans, we used a high-resolution brain-purpose SHR12000 (Hamamatsu Photonics KK, Hamamatsu, Japan) tomograph (intrinsic resolution, $2.9 \times 2.9 \times 3.4$ full-width half-maximum, 47 slices, 163 mm axial field of view). After setting the scanner's gantry parallel to the AC-PC line by tilting it, a 10-mins transmission scan for attenuation correction was performed using a $^{68}Ge/^{68}Ga$ source with the subject's head fixed by a radiosurgery purpose thermoplastic facemask, which enabled the head to be fixed to the same place between the first and second PET measurements among the same subjects. In the [$^{11}$C]CFT PET study, we performed serial scans (time frames: $4 \times 30$, $20 \times 60$, $14 \times 300$ secs) and periodical arterial blood sampling for 92 mins after injecting intravenously a 350-MBq dose of [$^{11}$C]CFT at a slow bolus taking 1 min (Ouchi *et al*, 1999*b*). To determine unchanged radioligand and radioactive metabolites, additional arterial blood samples were drawn at 1, 5, 20, 30, and 45 mins after the tracer injection and analyzed using thin-layer chromatography and a storage-phosphor-screen bioimaging analyzer (BAS-1500, Fuji Film, Tokyo, Japan). The free metabolite-corrected plasma activities were fitted to a sum of three exponentials by the non-linear least-squares method with the nonweighted Gauss–Newton algorithm. In the [$^{11}$C]raclopride study, PET measurement was performed after a time interval of 3 h to allow for the decay of radioactivity. Each participant with the subject's head fixated at the same position as in the [$^{11}$C]CFT study underwent dynamic PET scans ($4 \times 30$, $20 \times 60$, and $8 \times 300$ secs) for 62 mins after a slow bolus injection of a 300-MBq dose of [$^{11}$C]raclopride with periodical arterial blood sampling for metabolite correction (Ouchi *et al*, 2002).

### Data Analysis

Because various types of structural alterations including ventricular enlargement existed in this iNPH group, we first made a morphometric study for morphology of the midbrain and lateral ventricle. The ventricular dilatation was evaluated by Evans index larger than 0.3 (the ratio of the longest distance between the frontal horns of the lateral ventricles to the longest diameter of the right-to-left side of the brain) (Synek *et al*, 1976). We also measured the maximum oblique diameter of the midbrain from the aqueduct via the substantia nigra to the edge of cerebral peduncle and the maximum interpeduncular distance at the level of the substantia nigra and red nucleus (Doraiswamy *et al*, 1992; Ouchi *et al*, 2005), and the size of frontal horn of the lateral ventricle (O'Hayon *et al*, 1998) on the MR images. All morphometric values *except* for Evans index were expressed as ratios (percentage) to the maximal diameter between the frontal and occipital poles along the intercommissural line.

Then, multiple irregular ROIs (40 to 200 mm$^2$) were drawn bilaterally over the nucleus accumbens, ventromedial striatum (head of the caudate), the inferolateral (ventral putamen) and superodorsal parts (dorsal putamen) of the striatum, and the cerebellum on the MR images (Mai *et al*, 1997). These ROIs were then transferred onto the corresponding dynamic [$^{11}$C]CFT and [$^{11}$C]raclopride images with 6.8-mm slice-thickness data generated after adding two consecutive slices using image-processing software (Dr View, Asahi Kasei Co., Tokyo, Japan) on a SUN workstation (Hypersparc ss-20, SUN Microsystems, San Diego, CA, USA) (Ouchi *et al*, 1999*b*). A brain morphological change because of ventricular enlargement may cause an error of parameter estimation due to partial volume effect. However, this method of determining the ROIs based on individual MRI minimized the error and the pitfalls of applying a standardized normal brain template to the anatomically affected NPH brain (Owler *et al*, 2004; Giovacchini *et al*, 2005). Indeed, we performed a morphometric analysis for the ROI volumes to test any difference in volume because of the presence of structural atrophy in iNPH. A simple *t*-test revealed no significant difference in volume between the two groups (see Table 3). The values of bilateral ROIs for the cerebellum in the disease group and for all the regions examined in the control group were averaged for further analysis.

Because, as described in the PET procedure, participants were scanned in the same position between the two PET measurements, the same ROIs could be placed on both [$^{11}$C]CFT and [$^{11}$C]raclopride parametric images. This approach allowed us to examine both aspects of dopaminergic functions presynaptically and postsynaptically *in vivo*. The *BP*, $B_{max}'/k_d$ (or $k_3/k_4$) for [$^{11}$C]CFT was estimated based on the three-compartment model by fitting artery and tissue TACs for blood-brain barrier transport rates ($K_1$), the free plus nonspecific distribution volume (DV) ($K_1/k_2$), and the binding and dissociation rate constants ($k_3$ and $k_4$ respectively), as described elsewhere (Ouchi *et al*, 1999*a*). In addition, the BP for [$^{11}$C]raclopride was estimated using the following equation and the nonlinear least-squares fitting method; $B_{max}'/k_d$ = (target

tissue $V_d$)/(cerebellum $V_d$)−1, where each $V_d$ (DV) was obtained by the Logan graphical method (Logan *et al*, 1994; Ouchi *et al*, 2002). Although age-dependent decreases were reported in the binding for dopamine transporter and receptors (Antonini *et al*, 1993), we did not correct the BPs estimated for aging, because there was not a significant difference in age between groups in the present study ($P>0.05$, $\chi^2$ test).

### Statistics

For comparisons of [$^{11}$C]CFT and [$^{11}$C]raclopride binding levels between groups, two-way analysis of variance (ANOVA) was first performed to evaluate the levels about one inter-subject factor and the intra-subject factor (i.e., the hemispheric side of the basal ganglia nucleus) for evaluating the interhemispheric effect to exclude a possible entry of early parkinsonism in the present group. It was found that there was no significant interaction in the two-way ANOVA between the hemispheric side and types of group ($P>0.1$), and, therefore, all estimates were separately evaluated by one-way ANOVA in either region with Bonferroni's test for the correction of multiple comparisons. Statistical significance was given as $P<0.05$ because the *post hoc* multiple comparisons were performed in these analyses. The one-way ANOVA was also performed when analyzing the morphometric data. The multiple regression analyses between regional [$^{11}$C]CFT binding and [$^{11}$C]raclopride binding, and between the measures of the lateral ventricle or midbrain and the tracers' binding were performed within each group. Spearman's rank correlation analysis was used to compare psycho-behavioral scores with BPs of the two tracers in each region. The significance level was given as a *P*-value less than 0.05.

## Results

### Morphometric Evaluation of the Ventricle and Midbrain Sizes in the Idiopathic Normal Pressure Hydrocephalus Group

As shown in Table 2, the width of the lateral ventricle at the caudate head was significantly greater in the iNPH group, as expected. However, the measured distance of the midbrain in the iNPH group was found to be the same as that in the normal group (Table 2) albeit with a tendency to have a wider angle between the bilateral peduncles.

### The Levels of [$^{11}$C]2-β-carbomethoxy-3β-(4-fluorophenyl) tropane and [$^{11}$C]raclopride Binding Potentials

One-way ANOVA showed that the levels of BP for [$^{11}$C]raclopride were significantly lower in the nucleus accumbens (−34%) and putamen (−25%) in the iNPH group than in the healthy group ($P<0.05$). The BP level in the dorsal putamen decreased more than that in the ventral putamen.

**Table 2** MRI-based linear measurements (percentage)

| *Region* | *Level* | *NPH* | *Normal* |
|---|---|---|---|
| Lateral ventricle | Frontal horn width (R) | 14.3 (4.7)* | 3.2 (0.4) |
| | Frontal horn width (L) | 14.8 (5.1)* | 3.3 (0.6) |
| | Evans index | 37.3 (2.9)* | 23.3 (3.2) |
| Midbrain | Oblique diameter | 18.2 (1.6) | 17.1 (1.8) |
| | Interpeducular distance | 26.5 (3.1) | 24.4 (1.63) |

Results are all percentage values, expressed as mean (s.d.).
*$P < 0.05$ versus normal group (one-way ANOVA). R: right, L: left.

The statistics showed a tendency of reduction in the level of [$^{11}$C]raclopride BP in the caudate (−18%) in the iNPH group compared with the normal counterpart ($P=0.09$). In contrast, the magnitude of [$^{11}$C]CFT BP (−5% in average) was not significantly different between the two groups (Table 3). No differences in DV of [$^{11}$C]CFT and [$^{11}$C]raclopride were found between the two groups. There was no significant regional difference in magnitude of [$^{11}$C]raclopride BP among the dopamine projection areas in the iNPH group.

### Correlation Between [$^{11}$C]2-β-carbomethoxy-3β-(4-fluorophenyl) tropane and [$^{11}$C]raclopride Binding Potentials

Regression analyses showed a significantly positive correlation between [$^{11}$C]CFT and [$^{11}$C]raclopride binding in the dorsal putamen of the healthy group (Figure 1A, $y=0.22x+1.40$, $r^2=0.59$) and a negative correlation in the dorsal putamen of the iNPH group (Figure 1B, $y=-0.43x+2.78$, $r^2=0.51$). In the ventral putamen, there was a tendency of positive correlation in healthy subjects and negative correlation in iNPH patients.

### Comparison Between Psycho-Behavioral Scores and Binding Levels of two Tracers in the Nucleus Accumbens and Dorsal Putamen in Idiopathic Normal Pressure Hydrocephalus Patients

Correlation analyses showed a significantly positive correlation between [$^{11}$C]raclopride binding in the nucleus accumbens and emotion score (Figure 2A, $y=0.03x+0.70$, $r^2=0.52$) and a negative correlation between [$^{11}$C]raclopride binding in the dorsal putamen and navigation time (Figure 2B, $y=-0.08x+2.84$, $r^2=0.53$). However, there was no significant correlation between [$^{11}$C]CFT binding and these psycho-behavioral parameters. Figure 3 shows one example of this inverse association.

## Discussion

The present results for the first time show an asymmetric change in BPs of presynaptic and

**Table 3** Levels of binding potential for [$^{11}$C]CFT and [$^{11}$C]raclopride and ROI volume

| | | *DV* | *Binding potential* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *Cerebellum* | *Nucleus accumbens* | | *Caudate* | | *Ventral putamen* | | *Dorsal putamen* | |
| *Group* | *Tracer* | *Bilateral* | *Right* | *Left* | *Right* | *Left* | *Right* | *Left* | *Right* | *Left* |
| NPH | CFT | 8.14 (0.40) | 2.46 (0.69) | 2.49 (0.43) | 3.41 (0.68) | 3.26 (1.02) | 3.16 (0.56) | 3.27 (0.40) | 2.77 (0.59) | 2.91 (0.46) |
| | RAC | 0.41 (0.04) | 1.11* (0.18) | 1.17* (0.24) | 1.44 (0.24) | 1.58 (0.36) | 1.71* (0.47) | 1.72* (0.28) | 1.54* (0.26) | 1.58* (0.39) |
| N | CFT | 8.64 (0.50) | 2.96 (0.69) | | 3.18 (0.42) | | 3.48 (0.60) | | 2.89 (0.77) | |
| | RAC | 0.49 (0.07) | 1.77 (0.30) | | 1.89 (0.36) | | 2.23 (0.22) | | 2.06 (0.21) | |
| *ROI volume (cm$^3$)* | | | | | | | | | | |
| NPH | | 1.08 (0.27) | 0.40 (0.14) | 0.37 (0.13) | 0.48 (0.14) | 0.49 (0.11) | 0.96 (0.21) | 0.93 (0.20) | 0.82 (0.20) | 0.84 (0.22) |
| N | | 1.12 (0.26) | 0.45 (0.12) | | 0.51 (0.13) | | 1.00 (0.29) | | 0.85 (0.12) | |

Values are expressed as mean (s.d.). DV: distribution volume for the cerebellum.
*$P < 0.05$ versus normal group.

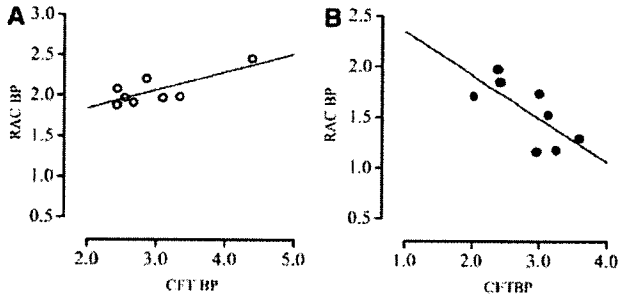


**Figure 1** Correlations between levels of [$^{11}$C]CFT and [$^{11}$C]raclopride BPs in the dorsal putamen in the healthy group (**A**) and idiopathic normal pressure hydrocephalus group (**B**).

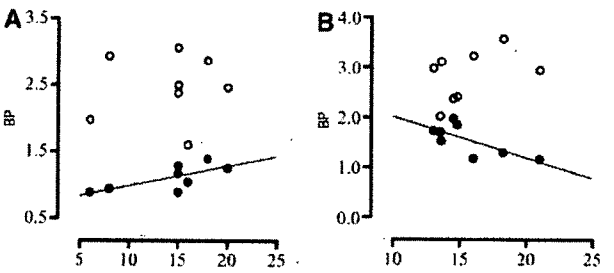


**Figure 2** Correlations of [$^{11}$C]CFT (open circle) and [$^{11}$C]raclopride (closed circle) BPs in the nucleus accumbens with emotional scores (abscissa) (**A**) and in the dorsal putamen with navigation time (abscissa) (**B**) in the iNPH group. Significant correlations were only found as for [$^{11}$C]raclopride binding.

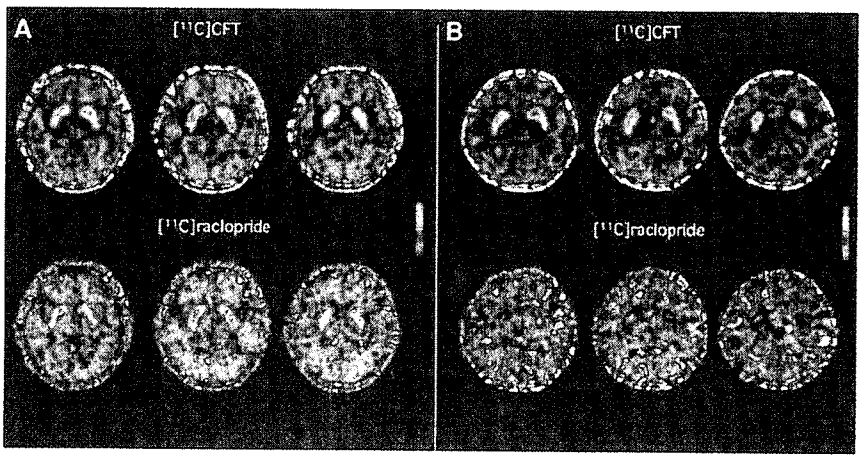


**Figure 3** Magnetic resonance imaging–positron emissiontomography fusion parametric images of [$^{11}$C]CFT and [$^{11}$C]raclopride binding normalized to the cerebellum in a 68-year-old healthy subject (**A**) and a 77-year-old patient with iNPH (**B**). A marked reduction in [$^{11}$C]raclopride binding was observed in the striatum bilaterally, while [$^{11}$C]CFT uptake was within normal limits in the iNPH patient although there might be a milder reduction of the binding in the putamen in a cranio-caudal fashion possibly due to age. Top row: [$^{11}$C]CFT images, bottom row: [$^{11}$C]raclopride images.

postsynaptic radiotracers and the clinical-pathophysiologic relevance of postsynaptic dopaminergic hypoactivity in the dorsal putamen to the severity of gait impairment in iNPH. This asymmetric pattern of tracers' binding is remarkably different from the opposite direction of the asymmetric change in PD; reduction in binding of the presynaptic marker and a tendency of upregulation of postsynaptic maker (Heiss and Herholz, 2006; Ouchi *et al*, 1999*a*), and parallel changes in those two tracers in normal aging and sporadic parkin-linked parkinsonism (Scherfler *et al*, 2004). This suggests that alteration in striatal postsynaptic dopaminergic function and preservation of nigral dopamine function may reflect a pathophysiology of iNPH.

The present normal finding of [$^{11}$C]CFT binding along with reduction in striatal [$^{11}$C]raclopride binding in iNPH patients indicates that the entity of iNPH resides chiefly in dysfunction in the dopamine projection area involved in the basal ganglia–cortical circuit. The previous reports, albeit in the experimental setting, showing that there was not significant reduction either in dopamine level (Del Bigio and Vriend, 1998) or dopaminergic nigral neurons (Ishizaki *et al*, 2000) in rats 4 weeks after induction of hydrocephalus support the present finding of preserved [$^{11}$C]CFT binding in iNPH patients. As for reduction in [$^{11}$C]raclopride binding, two explanations may be possible at the moment, downregulation and loss of the D2 receptors. The level of [$^{11}$C]raclopride binding at baseline varies in the pathophysiologic status of the disease or the amount of drug interaction on the D2 receptor. This is because in PD, upregulation of [$^{11}$C]raclopride binding to the receptor shown at an early stage of PD declines with the disease severity increasing (Antonini *et al*, 1995) and with dopamine agonists administered (Heiss and Herholz, 2006). Since all iNPH patients in the current study were naïve to drugs known to affect the D2 receptor (Table 1), it is confirmed that the present reduction in [$^{11}$C]raclopride binding reflects a pathophysiologic change characteristic of the disease. Although there is no histochemical study on alterations in D2 receptor in the striatum in chronic hydrocephalus, the presence of axonal injury in the white matter (Del Bigio *et al*, 2003) and a decrease in the number of cholinergic neurons (Ishizaki *et al*, 2000) in the rat neostriatum in the subacute hydrocephalic condition can exrapolate that loss of D2 receptors might be responsible for the reduction of [$^{11}$C]raclopride binding in the present study. This speculation is in line with the result that D2 receptor-lacking knockout mice exhibited a phenotype similar to the extrapyramidal symptoms of PD (Baik *et al*, 1995). Because D2 receptor mediates motor information from the cortex (Calabresi *et al*, 1997), either downregulation or loss of D2 receptors can impair the corticostriatal neuronal transmission in iNPH.

It is interesting that [$^{11}$C]raclopride binding in the caudate located closer to the enlarged ventricle was not significantly decreased than that in the dorsal putamen and nucleus accumbens in the present study. This may implicate that the vicinity to the dilated ventricle is not an important factor for the influence of [$^{11}$C]raclopride binding in iNPH. The caudate nucleus is principally connected to the frontal eye field (Gerardin *et al*, 2003). Thus, these findings support the rarity of disturbance in saccadic eye movement in iNPH patients clinically. In contrast, the dorsal part of the putamen chiefly received the neuronal input from the sensorimotor cortex (Kunzle, 1975). A recent functional MRI study has shown that the foot area is somatotopically located in the dorsal putamen (Gerardin *et al*, 2003). Our previous PET study with [$^{11}$C]raclopride showed that the foot motor execution increased dopamine release in this dorsal putamen (Ouchi *et al*, 2002). These lines of evidence support the present finding that [$^{11}$C]raclopride binding in the dorsal putamen significantly correlated with gait performance (navigation time) in iNPH patients because the connection between the sensorimotor cortex and the corresponding putaminal region might be disrupted anatomically and functionally. In addition, significant association of mood with nucleus accumbens [$^{11}$C]raclopride binding in our iNPH patients might be explained the same way because the prefrontal cortical input in the nucleus accumbens is modulated selectively by phasic dopamine release through the D2 receptor in regulation of motivation processing (Goto and Grace, 2005). These findings suggest that dopaminergic derangement in the 'motor' putamen and 'motivational' nucleus accumbens might be characteristic of iNPH pathophysiology.

Morphological alteration in the brain is an important sign to be considered for clinical diagnosis of iNPH. In the present study, in addition to significant dilatation of lateral ventricles, there was a tendency of flattening of the midbrain anteroposteriorly in the iNPH group, that is, a longer interpeduncular diameter with a wider angle between the bilateral crus cerebri on the horizontal MRI plane. This tendency was in line with a shorter anteroposterior diameter measured on the sagittal MR plane (Lee *et al*, 2005), in which the severity of gait disturbance was reported to correlate negatively with the midbrain diameter. In view of the dopaminergic activity, however, we did not see either significant reduction in the presynaptic ([$^{11}$C]CFT) marker binding or significant correlation between the marker binding and behavioral measures in the present study. Unlike the finding in PD showing that the midbrain pedunculopontine nucleus, known as a lower locomotion center, is degenerated (Pahapill and Lozano, 2000), there is no such evidence in iNPH. Furthermore, the average disease duration in our iNPH patients is found to be relatively short and gait disturbance milder, indicating that the cellular activities of dopamine neurons in the midbrain

can be spared at an early stage of iNPH despite ensuing deformity of the midbrain structure.

In summary, we showed significant reduction in the postsynaptic D2 receptor binding and preservation of the presynaptic dopamine transporter binding in the striatum of iNPH patients. The reduction of D2 receptor binding in the dorsal putamen (striatal foot area) may be pathophyiologically important for progressive gait deterioration in the disease. Alterations in D2 receptor control in the corticostriatal system may contribute to the clinical manifestations reminiscent of parkinsonism seen in iNPH.

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# Striatal $D_2$ Receptor Availability After Shunting in Idiopathic Normal Pressure Hydrocephalus

Teiji Nakayama[1], Yasuomi Ouchi[2], Etsuji Yoshikawa[3], Genichi Sugihara[4], Tatsuo Torizuka[2], and Keisei Tanaka[1]

*[1]Department of Neurosurgery, Hamamatsu Medical Center, Hamamatsu, Japan; [2]Positron Medical Center, Hamamatsu Medical Center, Hamamatsu, Japan; [3]Central Research Laboratory, Hamamatsu Photonics K.K., Hamamatsu, Japan; and [4]Department of Psychiatry, Hamamatsu University School of Medicine, Hamamatsu, Japan*

Gait disturbance in idiopathic normal pressure hydrocephalus (iNPH) is reminiscent of parkinsonism. Our recent PET study showed reduction in postsynaptic $D_2$ receptor binding concomitant with a normality of presynaptic dopamine transporter binding. Here, we investigated the plasticity of $D_2$ receptor in treating iNPH patients with ventriculoperitoneal (VP) shunting using PET with $^{11}$C-raclopride and discuss the contribution of $D_2$ receptor to the pathophysiology of iNPH. **Methods:** Eight iNPH patients participated in this study. After evaluation of their neuropsychologic abilities, all patients underwent 3-dimensional MRI and quantitative PET measurements twice before and 1 mo after VP shunting. MRI-based morphometric analyses were performed to examine postoperative variations of the ventricles. Estimation of binding potential (BP) for $^{11}$C-raclopride was based on Logan plot analysis. Region-of-interest analysis was used to examine changes in $^{11}$C-raclopride BP in the striatum. A 2-tailed paired *t* test was used for evaluating changes in PET and MRI parameters between conditions, and correlation analysis was used to investigate clinicopathophysiologic relevance (clinical vs. in vivo findings). **Results:** Clinical evaluation revealed significant recovery in a 5-m back-and-forth navigation test and an affect test and a mild increase in Mini-Mental State Examination scores after VP shunting. Significant postoperative increases in $^{11}$C-raclopride BP were found in the nucleus accumbens and dorsal putamen, and the increases were significantly associated with emotional (Spearman rank $r = 0.66$, $P < 0.05$) and navigational improvement ($r = 0.72$, $P < 0.05$), respectively. The $^{11}$C-raclopride BP increase in the striaum as a whole correlated significantly with improvement in general cognitive ability. There was a mild ventricular shrinkage after surgery, albeit there was no correlation of its size with clinical and PET parameters. **Conclusion:** Striatal upregulation of $D_2$ receptor after VP shunting is associated with amelioration of hypokinetic gait disturbance and anhedonic mentation in iNPH patients, indicating that the effect of VP shunting may reside in noninhibition of functionally suppressed $D_2$ receptor in the striatum. $D_2$ receptor responsiveness may indicate a mechanism for iNPH pathophysiology.

**Key Words:** idiopathic normal pressure hydrocephalus; $D_2$ receptor; raclopride; ventriculoperitoneal shunting; PET

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The clinical triad for idiopathic normal pressure hydrocephalus (iNPH) consists of gait disturbance, progressive dementia, and urinary incontinence (*1*), which develop insidiously without causative disorders (*2*). In the clinical setting, gait disturbance is likely the first sign and important symptom in NPH (*3*). However, this hypokinetic type of gait disturbance is not unique in other neurologic diseases such as Parkinson's disease (PD) and dementia with extrapyramidal symptoms. To diagnose iNPH, a spinal tap is considered prerequisite, and empirically its effect on gait improvement is the most remarkable (*4*). Our previous study highlighted a close relationship of gait impairment with putaminal $D_2$ receptor downregulation in iNPH (*5*). In this study, we investigated whether the reduction in $D_2$ receptor activity is constant even after ventriculoperitoneal (VP) shunting.

The effect of VP shunt surgery on cerebral glucose metabolism is reportedly inconsistent (*6*), but increases in cerebral glucose metabolism (*7*) and cerebral vascular response (*8*) after shunting are likely to parallel clinical improvement in iNPH. Experimental animal studies showed that kaolin-induced reductions in regional cerebral blood flow in kitten (*9*) and immunoreactivity of subsatatia nigral neurons in rats (*10*) were restored by VP shunting. Despite these lines of studies, the VP shunt effect on the neurotransmitter system—especially the dopaminergic system, which is important for psychomotor control—remains to be investigated. Therefore, the present study, using PET with $^{11}$C-raclopride in combination with evaluation of clinical variables before and after the surgery, was designed to test whether the reduced $D_2$ receptor activity in the striatum can be restored by VP shunting.

## MATERIALS AND METHODS

### Patients

We studied 8 patients with iNPH who were all naïve to dopaminergic drugs (5 men, 3 women: mean age ± SD, 74.9 ± 2.0 y

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For correspondence or reprints contact: Yasuomi Ouchi, MD, PhD, Human Imaging Research Laboratory, Molecular Imaging Frontier Research Center, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan.
E-mail: ouchi@pmc.hmedc.or.jp

[range, 72–77 y]; Table 1) and whose diagnoses were based on the clinical and imaging features: gait disturbance, cognitive impairment, sphincter control problem, normal lumber cerebrospinal fluid (CSF) pressure < 20 cm $H_2O$ (*1,11*), ventricular enlargement in the brain, and reduced cortical sulcal space in the superior convexity on coronal viewing of MR images (*12*). We excluded patients who showed any degree of extrapyramidal symptoms such as rigidity or tremors reminiscent of PD. In addition, a positive response in CSF tap tests*(*13*) after PET measurement confirmed the inclusion of patients with iNPH in the current study. The CSF flow after shunting was controlled using a Codman–Hakim programmable valve system. The current study was approved by the local Ethics Committee of the Hamamatsu Medical Center, and written informed consent was obtained from all participants after a full explanation of the nature of the study.

### Psychobehavioral Assessment

As described previously (*5*), before each PET measurement, all patients received a general cognition test (Mini-Mental State Examination [MMSE]; full score = 30) and an affect test regarding basic affects: happiness, sadness, surprise, disgust, anger, and fear (full score = 20) using cards with different cartoon facial expressions similar to the computer graphics pictures (*14*), and they underwent a 5-m back-and-forth navigation test (*2*) before and after surgery. Our preliminary examination showed that 11 healthy subjects (mean age = 50.4 y) scored more than 28 on the MMSE, scored 20 on the affect test, and took less than 10 s in the back-and-forth walk (data not shown).

### Scanning Procedures

Each patient underwent a morphologic MRI study twice before and after shunting using a static magnet (0.3-T MRP7000AD; Hitachi) with 3-dimensional mode sampling (acquisition parameters: repetition time/echo time, 200/23; 75° flip angle; 2-mm slice thickness with no gap; 256 × 256 matrices) to evaluate the volumetric changes of the ventricles and to determine the striatal nuclei for setting the regions of interest (ROIs). After the second MRI after surgery, the altered flow of CSF in the VP shunt system was reset to presurgery levels.

The detail of the PET procedure was also described elsewhere (*5*). In brief, PET was performed using a high-resolution brain-purpose PET camera (SHR12000, Hamamatsu Photonics K.K.; 24 detector rings yielding 47 slices simultaneously; spatial resolution, 2.9 mm; full width at half maximum, 163-mm axial field of view) (*15*), which acquired imaging data parallel to the anterior commissure–posterior commissure line. After the filtered back-projection (Hanning filter), the reconstructed image resolution became 6.0 × 6.0 × 3.2-mm full width at half maximum, and each resulting voxel measured 1.3 × 1.3 × 3.4 mm. In the first PET study, after acquiring the transmission scan for attenuation correction, serial dynamic scans and periodic arterial blood sampling were performed for 62 min after a slow bolus injection (5-mL total volume) of 370 MBq $^{11}$C-raclopride with a specific activity of more than 37 GBq/μmol. Additional arterial blood samples were collected for determination of radioactive metabolites used in a model-based estimation of the binding potential (BP) of the tracer. One month after VP shunting, the second postsurgery PET was performed in the same way as in the first scan except for omission of arterial blood sampling.

**TABLE 1**
Clinical Features of Each Patient Before and After Shunting

| Patient no. | Age (y) | Sex | DD | MMSE | | Gait time | | UI score | | AT score | | LCSF | Medication |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Before | After | Before | After | Before | After | Before | After | Before | |
| 1 | 77 | F | 1.1 | 14 | 15 | 21.9 | 16.9 | 3 | 2 | 9 | 10 | 11 | Anti-HT, anti-DM |
| 2 | 74 | M | 2.5 | 23 | 23 | 16.2 | 12.8 | 2 | 2 | 15 | 16 | 10 | None |
| 3 | 74 | M | 6.8 | 25 | 26 | 14.5 | 10.7 | 2 | 1 | 15 | 16 | 9 | Anti-HT |
| 4 | 72 | M | 1.0 | 26 | 25 | 12.6 | 11.7 | 1 | 2 | 17 | 18 | 12 | Anti-HT |
| 5 | 76 | F | 3.0 | 21 | 22 | 16.4 | 14.6 | 2 | 1 | 16 | 17 | 10 | Antipollakiuria |
| 6 | 77 | F | 2.0 | 20 | 21 | 18.3 | 14.9 | 0 | 0 | 16 | 17 | 11 | Anti-HT |
| 7 | 76 | M | 1.3 | 15 | 15 | 26.2 | 20.2 | 2 | 2 | 17 | 17 | 14 | None |
| 8 | 73 | M | 1.0 | 26 | 27 | 31.3 | 24.8 | 2 | 2 | 15 | 16 | 12 | None |
| Mean (SD) | 74.9 (1.9) | | 2.3 (2.0) | 21.3 (4.7) | 21.8 (6.2) | 19.7 (6.4) | 15.8 (4.7) | 1.7 (0.9) | 1.5 (0.8) | 15.0 (2.6) | 15.9 (2.5) | 11.1 (1.6) | — |

DD = disease duration (y) from onset to PET measurement; MMSE = Mini-Mental State Examination; gait time = time (s) for walking 5 m back and forth; UI = urinary incontinence score (0 = none, 1 = present without wearing diaper, 2 = present occasionally while wearing diaper, 3 = diaper requisite); AT score = affect test with full score of 20; LCSF = lumber CSF pressure (cm $H_2O$); anti-HT = antihypertensive drug; anti-DM = antidiabetes mellitus drug.

### Data Analysis

In MRI analysis, we first tested whether postsurgery morphologic changes in the ventricles were present in the MR images on the basis of a previous method (*5*). Briefly, we measured the degree of the ventricular dilatation as an Evans' index (*16*) and the size of the frontal horn of the lateral ventricle (*17*) on the MR images.

In PET analysis, multiple irregular ROIs were drawn bilaterally over the nucleus accumbens, the ventromedial striatum (head of the caudate), the inferolateral (ventral putamen) and superodorsal parts (dorsal putamen) of the striatum, and the cerebellum on the MR images (*18*). These ROIs were then transferred onto the corresponding dynamic $^{11}$C-raclopride images with 6.8-mm slice-thickness data generated after adding 2 consecutive slices using image-processing software (Dr View; Asahi Kasei Co.) on a Sun workstation (Hypersparc ss-20; Sun Microsystems) (*19*). A morphologic change in the brain due to a variety of ventricular enlargement may cause an error of parameter estimation because of the partial-volume effect. However, the ROI method using individual MRI minimizes the error and the pitfalls of applying a standardized normal brain template to the anatomically distorted NPH brain (*20,21*). The BP for $^{11}$C-raclopride was estimated on the basis of the invasive Logan graphical analysis in the first PET study and on its noninvasive analysis in the second PET study, in which the rate constant $k_2$ was assumed to be the same value as $k_2$ estimated in the first model (*22,23*). Percentage differences (%Δ) in BP and psychobehavioral scores between preoperative and postoperative conditions were calculated as follows: %Δ = (postoperative − preoperative)/preoperative × 100.

### Statistical Analysis

To test changes in MR morphometric measures and BPs after shunting, the 2-tailed, paired Student *t* test was used. Psychobehavioral scores between conditions were compared using a 1-tailed, paired Student *t* test. Spearman rank correlation was tested between psychobehavioral scores and BPs in each region. The significance level for all statistics was defined as a $P$ value $< 0.05$.

## RESULTS

### Psychobehavioral Changes After Shunting

As shown in Table 1, there was significant improvement in the navigation time scores (%Δ = 18.8% ± 6.5%) and the affect scores (%Δ = 5.4% ± 3.7%) ($P < 0.05$, paired *t* test). A slight increase was found in the MMSE scores (%Δ = 2.6% ± 3.6%) but not in the micturition scores (%Δ ≈ 0%) after shunting. No patients had postoperative deterioration in their daily activities.

**TABLE 2**
MRI-Based Morphometric Changes After Shunting

| Parameter | Before surgery | After surgery | %Δ |
|---|---|---|---|
| Frontal horn width (right) | 15.0 (5.5) | 14.2 (5.4) | −6.2 (4.4) |
| Frontal horn width (left) | 15.7 (6.0) | 14.6 (5.4) | −6.5 (2.5) |
| Evans' index | 37.6 (1.9) | 36.8 (1.6) | −2.1 (1.0) |

%Δ = percentile change.
Results are percentage values, expressed as mean (SD).

### Morphometric Measures

As shown in Table 2, MRI-based morphometric measures did not show any significant changes in size, although a slight tendency for reduction in the lateral ventricles was observed (about 6% reduction).

### $^{11}$C-Raclopride BPs

As shown in Table 3, the paired Student *t* test showed that the levels of BPs for $^{11}$C-raclopride were significantly higher in the nucleus accumbens bilaterally, dorsal putamen bilaterally, and left ventral putamen after shunting ($P < 0.05$).

### Correlation Between In Vivo Parameters and Clinical Improvement

Spearman rank correlation analysis showed a significantly positive correlation between percentile changes (%Δ) in $^{11}$C-raclopride BP after surgery in the left nucleus accumbens and the affect score (Fig. 1A, $y = 2.76x + 0.71$, $r^2 = 0.43$), and a more robust correlation between the changes in the dorsal putamen and the navigation time (Fig. 1B, right: $y = 0.78x - 6.23$, $r^2 = 0.56$; left: $y = 1.23x - 8.62$, $r^2 = 0.45$). In addition, the averaged $^{11}$C-raclopride BP change in the whole striatum was found to correlate positively with a rise in the MMSE scores (Fig. 1C, right:

**TABLE 3**
Changes in BP for $^{11}$C-Raclopride Before and After Shunting

| Condition | Nucleus accumbens | | Caudate | | Ventral putamen | | Dorsal putamen | |
|---|---|---|---|---|---|---|---|---|
| | Right | Left | Right | Left | Right | Left | Right | Left |
| Before surgery | 1.15 (0.22) | 1.10 (0.18) | 1.42 (0.32) | 1.40 (0.34) | 1.65 (0.21) | 1.61 (0.32) | 1.41 (0.19) | 1.42 (0.21) |
| After surgery | 1.31* (0.18) | 1.25* (0.14) | 1.47 (0.40) | 1.43 (0.43) | 1.70 (0.23) | 1.83* (0.32) | 1.51* (0.20) | 1.62* (0.21) |
| %Δ | 15.6 | 15.3 | 5.4 | 3.8 | 3.7 | 15.2 | 8.5 | 14.5 |

*$P < 0.05$ vs. before surgery (paired *t* test).
Values are expressed as mean (SD).

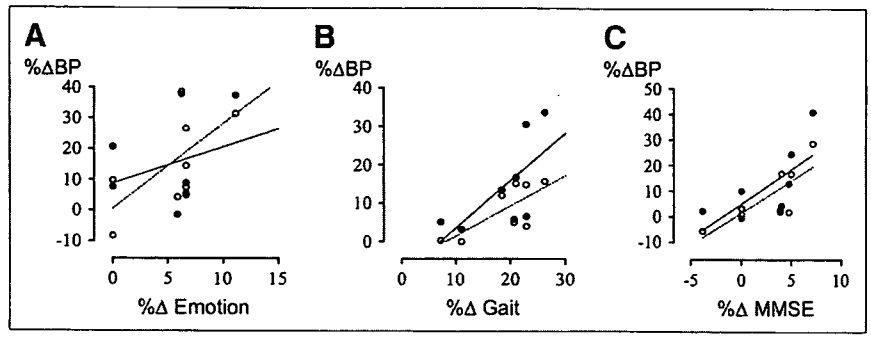


**FIGURE 1.** Correlations of emotional cognition changes with $^{11}$C-raclopride BP changes in nucleus accumbens (A), of navigation time changes with those in dorsal putamen (B), and of MMSE score changes with those in whole striatum (C) on right (○, dotted line) and left (●, solid line) side of brain.

$y = 2.51x + 1.71$, $r^2 = 0.62$; left: $y = 2.68x + 5.16$, $r^2 = 0.46$).

## DISCUSSION

This study shows that $D_2$ receptor availability was enhanced by VP shunting in iNPH and that this increase was associated with clinical improvements in gait and cognition, which are characteristically compromised in this disease. This resiliency of $D_2$ receptor availability in iNPH may be an explanation for the observed clinical recovery, especially in gait performance and emotional drive. Because of this recovery, iNPH may be referred to as a "treatable dementia."

The reduction in $^{11}$C-raclopride binding at baseline in iNPH may be explained by 2 mechanisms: downregulation or loss of $D_2$ receptors. Although the elevation of endogenous synaptic dopamine competes with $^{11}$C-raclopride binding and reduces its PET signal (*23,24*), a significant increase in dopamine release was unlikely in the present study because the basal level of the presynaptic marker $^{11}$C-2β-carbomethoxy-3β-(4-fluorophenyl) tropane ($^{11}$C-CFT) does not change in iNPH patients (*5*) and because the content of a monoamine metabolite, homovalinic acid, is reportedly lower in ventricular CSF (*25*). Considering that the $D_2$ receptor is involved in relaying motor information from the cortex (*26*), downregulation of $D_2$ receptor is a more likely explanation for the observed reduction of $^{11}$C-raclopride binding. Because the level of glutamate is reportedly elevated in the ventricular CSF of the hydrocephalic brain (*27*), it is possible that long-term excitability caused by excessive glutamate in the cortex perturbs dopamine release in the striatum (*28*), leading to downregulation of the postsynaptic $D_2$ receptor and attenuation of $D_2$ receptor function. One report on humans suggesting the presence of a metabolically hyperactive condition in the hydrocephalic brain (*29*) is in line with this cerebral excitability. In addition to this functional alteration theory, the loss of axons in the white matter (*30*), the reduced number of the rat striatal cholinergic neurons (*31*), and the finding that PD-like extrapyramidal signs were seen in $D_2$ receptor–lacking knockout mice (*32*) all support the

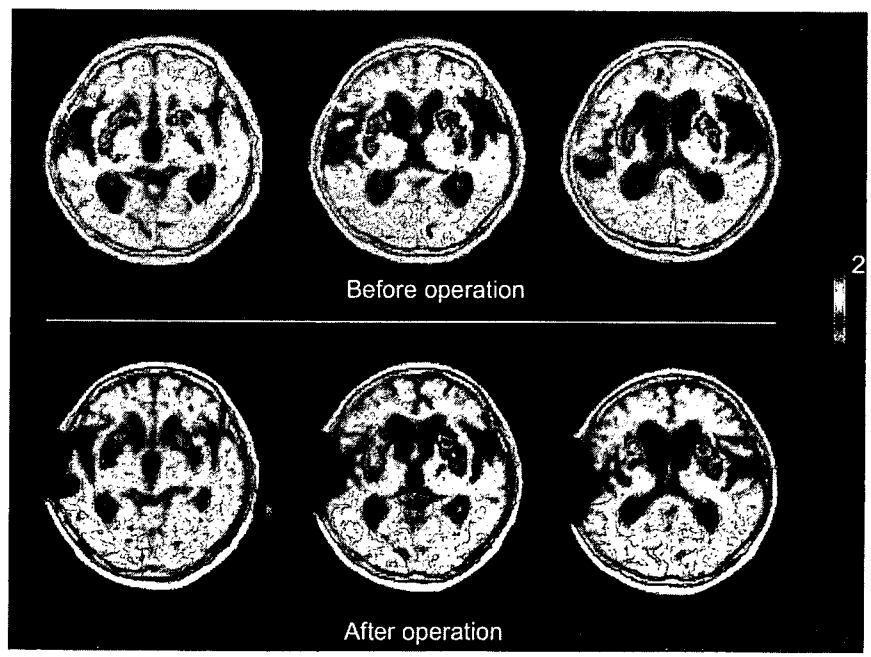


**FIGURE 2.** PET/MRI fusion parametric images of quantitative $^{11}$C-raclopride BP in an iNPH patient before and after shunting. Color bar denotes BP for $^{11}$C-raclopride (0–2).

possibility of DA neuronal loss. Therefore, downregulation or loss of $D_2$ receptors may be significantly involved in the impairment of corticostriatal neuronal transmission in iNPH.

In the present study, iNPH $D_2$ receptor downregulation was attenuated at 1 mo after VP shunt surgery (Fig. 2 illustrates an example of this phenomenon). A previous PET study showing significant increases of glucose metabolism in the cerebral cortical areas after surgery in iNPH (*7*) and a microdialysis study showing a postoperative reduction in the glutamate content of the cerebral cortex in iNPH patients (*33*) indicate that VP shunting may augment cortical neuronal activities partly by inhibiting neurotoxic effects in the cerebral cortex. This, in turn, could have stimulated dopamine release (*28*) and enhanced the activity of the $D_2$ receptor in the striatum in the present study. Postoperative recovery of gait and emotion were related to the responsiveness of regional $D_2$ receptor in the striatum, which was in line with findings that the dorsal putamen is involved in foot movement (*23,34*) and the nucleus accumbens is involved in higher motivation processing (*35*). The presence of variations of CSF dopamine metabolite content in responders and nonresponders to shunting (*36*) suggests a varying degree of stimulation of postsynaptic dopamine neurons after shunting.

The limitation of the present study is the observation of PET and clinical variables at one time point. It was reported that patients continued to improve for up to 24 mo, and about half of the initially improved patients had subsequent deterioration (*37*). This indicates that the time of our study was within the period of brain plasticity in progress, possibly potentiated by shunting. In this respect, additional PET with $^{11}$C-raclopride may be of great value for further clarification of changes in $D_2$ receptor availability during clinical deterioration in the decision of reintroduction of shunt surgery.

## CONCLUSION

In summary, we show regional upregulation of postsynaptic $D_2$ receptors concomitant with clinical improvement 1 mo after VP shunting of iNPH patients. Therefore, the $D_2$ receptor might be a potential therapeutic target in iNPH.

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# Validation of the Telephone Interview for Cognitive Status (TICS) in Japanese

Yoko Konagaya[1]*, Yukihiko Washimi[2], Hideyuki Hattori[2], Akinori Takeda[2], Tomoyuki Watanabe[1] and Toshiki Ohta[2]

[1]*Obu Dementia Care Research and Training Center, Obu, Japan*
[2]*National Center for Geriatrics and Gerontology, Obu, Japan*

## SUMMARY

**Background** In recent years, the population of elderly people in Japan with dementia has increased. Detection of cognitive impairment in the early stages is important for adequate treatment, care, and prevention.
**Aim** To investigate whether the reliability and validity of the instrument would carry over to a different population and language before using it for population-based epidemiological studies.
**Methods** We studied 135 subjects, 49 patients with Alzheimer's disease (AD) and 86 healthy controls (CTL) using the Telephone Interview for Cognitive Status (TICS) and developed the Japanese version of the TICS (TICS-J). We also evaluated combination of another telephone battery, the Category Fluency Test (CF).
**Results** The sensitivity and specificity of the TICS-J to differentiate AD patients from CTL was 98.0% and 90.7%, respectively. Pearson's correlation coefficient for the TICS-J and Mini-Mental State Examination (MMSE) was 0.858 ($p < 0.001$). On the Receiver Operating Characteristic (ROC), the area under the curve for the TICS-J was 98.7%. The combination of the TICS-J with the CF did not change the validity of the discrimination.
**Conclusion** These results indicated that TICS-J was a sensitive and specific instrument for differentiating AD patients from healthy controls. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — telephone interview; cognitive assessment; Alzheimer's disease; category fluency; TICS-J

## INTRODUCTION

In 2005, dementia was diagnosed in about 1,690,000 people in Japan, and the number is predicted to increase to 2,500,000 by 2015. Thus, detection of cognitive impairment in the early stages is important for adequate treatment, care, and prevention.

Cognitive function is important in epidemiological studies of elderly populations. The Mini Mental State Examination (MMSE) is one of the most widely used screening instruments to assess cognitive status (Folstein *et al.*, 1975). However, it requires face-to-face administration, and cannot be used with persons with visual deficits or some physical disabilities. The ceiling effect also limits the usefulness of the MMSE. Screening large populations for cognitive function is time-consuming and costly because of the face-to-face interviews. Also, elderly people often have a variety of physical impairments or minimal motivation that affects the results of any study.

The Telephone Interview for Cognitive Status (TICS) is a brief test of cognitive function administered via telephone for use in large-scale screenings and epidemiologic surveys (Brandt *et al.*, 1988). The TICS does not require vision or reading and writing, thus it is ideal for assessing cognitive function of illiterate persons or individuals with visual impairments (Mangione *et al.*, 1993). The TICS is a reliable, simple instrument for cognitive assessment in research and clinical practice.

The TICS consists of 11 test items, orientation, attention, short-term memory, repetition, comprehension and

*Correspondence to: Dr Y. Konagaya, Obu Dementia Care Research and Training Center, 3-294 Hantsuki-cho, Obu city, 474–0037, Japan. E-mail: y.konagaya.o-dcrc@dcnet.gr.jp



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conceptual knowledge, mathematical skills and praxis. It correlates highly with the MMSE, has high test–retest reliability, and its sensitivity and specificity for the detection of cognitive impairment are excellent.

The Category Fluency test (CF) measures long-term semantic memory, which is impaired in AD. The CF requires similar items in a semantic category; it is adequate for telephone administration and may complement the TICS.

The TICS has been translated into several foreign languages, including Spanish (Desmond *et al.*, 1994; Gude Ruiz *et al.*, 1994), Italian (Ferrucci *et al.*, 1998) and Finnish (Järvenpää *et al.*, 2002). Japanese language, including the culture, the social systems and education is quite different from the languages and cultures of countries of Europe. So, it is important to verify whether the telephone battery is acceptable and useful for Japanese people. In this study, we developed the Japanese version of the TICS (TICS-J) and evaluated its reliability and validity separately and with a combination of TICS-J and CF.

## SUBJECTS AND METHODS

### *Study population*

Participants selected from the Memory Clinic of the National Hospital for Geriatric Medicine, National Center for Geriatrics and Gerontology, consisted of 49 outpatients with Alzheimer's disease (AD) [19 men and 30 women, average age: 75.2 ± 6.8 years (mean ± SD)]. Diagnosis of AD was based on the criteria from the DSM-IV and NINCDS-ADRDA and was based on a general medical examination, neurological examination, laboratory tests, brain magnetic resonance imaging (MRI), brain single photon emission computed tomography (SPECT), and neuropsychological examination. All AD subjects had sufficient auditory function for telephone assessment.

The controls (CTL) were 92 healthy volunteers aged 60 or older with no acute or terminal conditions who were not taking drugs affecting cognitive function. Most control subjects were urban residents. Of these, six persons were excluded because they could not complete the TICS-J due to hearing impairments. Consequently 86 controls were analyzed for the following study [15 men and 71 women; average age: 74.3 ± 7.2 years] (Table 1).

The mean level of education was 11.0 ± 3.0 (mean ± SD) years for AD and 11.4 ± 2.2 years for CTL, and no significant differences were observed (Table 1). Informed consent was obtained from all subjects.

### *TICS-J*

The translation and back-translation were conducted by two neurologists and an English-Japanese translator. Minor modifications were made with the permission of the author to make the questions more suitable for the Japanese society and culture. The maximum score on the TICS-J was 41, which was the same as the original TICS.

### *CF*

Subjects were asked to name as many vegetables as possible in 1 min. All responses were recorded, and the scores were the sum of the new items, excluding preservations and intrusions.

### *Procedure*

All participants were initially screened by the MMSE, and 2 weeks later, the TICS-J and CF were administered by the same interviewer as with the MMSE. TICS-J was repeated 4 weeks later to some participants for test–retest reliability. The interviewers,

Table 1. Characteristics of AD and CTL groups

| | AD ($n=49$) | CTL ($n=86$) | $p$-value |
|---|---|---|---|
| Gender [men/women] | 19/30 | 15/71 | <0.001* |
| Age [years, mean ± SD, (range)] | 75.2 ± 6.8 (62–89) | 74.3 ± 7.2 (60–90) | 0.465[a] |
| Education [years, mean ± SD, (range)] | 11.0 ± 3.0 (6–17) | 11.4 ± 2.2 (6–16) | 0.405[b] |
| MMSE [points, mean ± SD, (range)] | 20.6 ± 4.6 (11–29) | 28.7 ± 1.2 (24–30) | <0.001[†] |
| TICS-J [points, mean ± SD, (range)] | 26.1 ± 6.1 (12–34) | 36.4 ± 2.3 (31–41) | <0.001[b] |
| Category Fluency [mean ± SD, (range)] | 7.7 ± 4.5 (0–20) | 14.1 ± 3.6 (7–26) | <0.001[a] |
| Time [seconds, mean ± SD, (range)] | 473.1 ± 121.9 (263–720) | 328.8 ± 60.4 (205–591) | <0.001[b] |

*Chi-square test.
[a]*t*-test.
[b]Mann–Whitney *U*-test.




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all well-trained professionals, informed the participant that the use of pens, pencils, papers, newspapers or calendars was not allowed as sources of orientation (Brandt and Folstein, 2003).

### *Statistical analysis*

The Kolmogorov-Smirnov normal evaluation was performed for each item. For items that ensured normality, Student's *t*-test was used, and for items that did not ensure normality, the Mann–Whitney *U*-test was used. Test–retest reliability was evaluated by the Intraclass Correlation Coefficient (ICC). The correlation between MMSE and TICS-J was calculated by Pearson's correlation coefficient. The areas under the curves on the Receiver Operating Characteristic (ROC) for the MMSE and TICS-J were generated to plot the advantages/disadvantages of sensitivity and specificity.

## RESULTS

The mean cognitive scores for the MMSE, TICS-J, and CF and the testing time in CTL by gender, age, and years of education are presented in Table 2. There were no differences in mean MMSE scores, TICS-J scores, CF scores, and testing time between men and women, among the different age groups, and between the low and high education groups.

The mean score for the MMSE was significantly low in AD ($20.6 \pm 4.6$ points, maximum 30) compared with CTL ($28.7 \pm 1.2$ points) ($p < 0.001$). The mean score for the TICS-J was also significantly low in AD ($26.1 \pm 6.1$ points, maximum 41) compared with CTL ($36.4 \pm 2.3$ points) ($p < 0.001$). The mean TICS-J testing time per individual was significantly longer in AD ($473.1 \pm 121.9$ sec) compared with that in CTL ($328.8 \pm 60.4$ sec) ($p < 0.001$) (Table 1). The scores from the CF were significantly lower in AD ($7.7 \pm 4.5$ points) compared with CTL ($14.1 \pm 3.6$ points) ($p < 0.001$)(Table 1).

The MMSE scores ranged from 11 to 29 points in AD, and in CTL the scores ranged from 24 to 30 points, showing a ceiling effect. The distribution of the TICS-J in AD was 13 to 34 points. Normal distribution for the TICS-J was shown in CTL (Figure 1a, b, c, d).

As to test–retest reliability of the TICS-J performed 4 weeks apart with 47 subjects (14 AD and 33 CTL), intra-class correlation (ICC) was calculated as 0.946 ($p < 0.001$).

The correlation between the TICS-J score and the MMSE score for the whole group was excellent ($r = 0.858$, $p < 0.001$), whereas it was 0.742 ($p < 0.001$) in the AD group only (Figure 2).

When choosing the cutoff score of 26 points for the MMSE, sensitivity was 91.8% and specificity was 95.3%. The cutoff score of 33 points for the TICS-J resulted in a sensitivity of 98.0% and a specificity of 90.7%.

When ROC curves were constructed, the area under the curve for the MMSE was 97.2% (95% Confidence Intervals (CI): 94.4%–100%), and 98.7% for the TICS-J (95% CI: 97.5%–100%) (Figure 3).

To determine whether or not the telephone battery could be improved, the CF was combined with the TICS-J. When choosing the cutoff score of 43 points for the TICS-J plus the CF, sensitivity was 85.7% and specificity was 93.0%.

The ROC curve in Figure 4 displays the TICS-J plus CF sensitivity-specificity data. The area under the curve was 95.9% for the TICS-J plus CF.

## DISCUSSION

In the population of elderly people in Japan, it is important to detect cognitive impairment in the early

Table 2. Characteristics of CTL group by gender, age and education (CTL group: $n = 86$)

| | MMSE* | TICS-J* | CF* | Time[a] |
|---|---|---|---|---|
| Gender | | | | |
| men ($n = 15$) | $28.8 \pm 0.8$ (28–30) | $35.1 \pm 2.2$ (32–40) | $11.7 \pm 2.8$ (7–18) | $325.1 \pm 55.2$ (205–415) |
| women ($n = 71$) | $28.6 \pm 1.3$ (24–30) | $36.7 \pm 2.2$ (31–41) | $14.6 \pm 3.5$ (7–26) | $329.6 \pm 61.8$ (220–591) |
| Age (years) | | | | |
| <70 ($n = 25$) | $28.8 \pm 1.1$ (26–30) | $36.5 \pm 2.2$ (31–40) | $14.8 \pm 3.1$ (7–19) | $310.9 \pm 53.3$ (205–479) |
| 70–79 ($n = 37$) | $28.8 \pm 1.2$ (27–30) | $36.9 \pm 2.5$ (32–41) | $14.3 \pm 3.5$ (8–26) | $327.0 \pm 59.6$ (220–591) |
| +80 ($n = 24$) | $28.3 \pm 1.5$ (24–30) | $35.6 \pm 2.1$ (32–40) | $13.0 \pm 3.9$ (7–20) | $350.3 \pm 64.3$ (266–488) |
| Education (years) | | | | |
| <10 ($n = 20$) | $28.8 \pm 1.1$ (27–30) | $36.0 \pm 2.5$ (32–40) | $13.6 \pm 3.0$ (10–19) | $327.5 \pm 47.6$ (263–439) |
| +10 ($n = 66$) | $28.6 \pm 1.3$ (24–30) | $36.6 \pm 2.2$ (31–41) | $14.2 \pm 3.7$ (7–26) | $329.2 \pm 64.1$ (205–591) |

*Points, mean ± SD, (range).
[a]Seconds, mean ± SD, (range).