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 ($P>0.05$, χ^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.

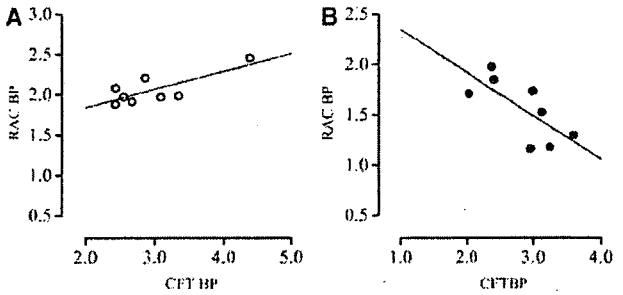

Figure 1 Correlations between levels of [^{11}C]CFT and [^{11}C]raclopride BPs in the dorsal putamen in the healthy group (**A**) and idiopathic normal pressure hydrocephalus group (**B**).

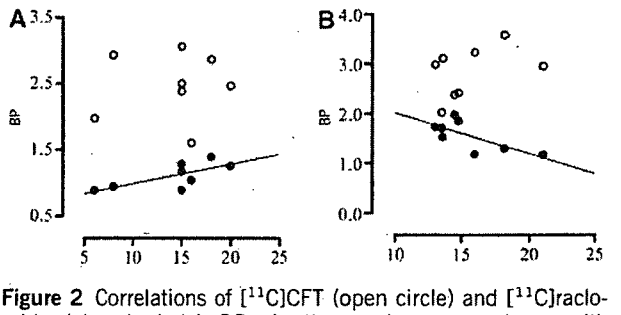

Figure 2 Correlations of [^{11}C]CFT (open circle) and [^{11}C]raclopride (closed circle) BPs in the nucleus accumbens with emotional scores (abscissa) (**A**) and in the dorsal putamen with navigation time (abscissa) (**B**) in the iNPH group. Significant correlations were only found as for [^{11}C]raclopride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

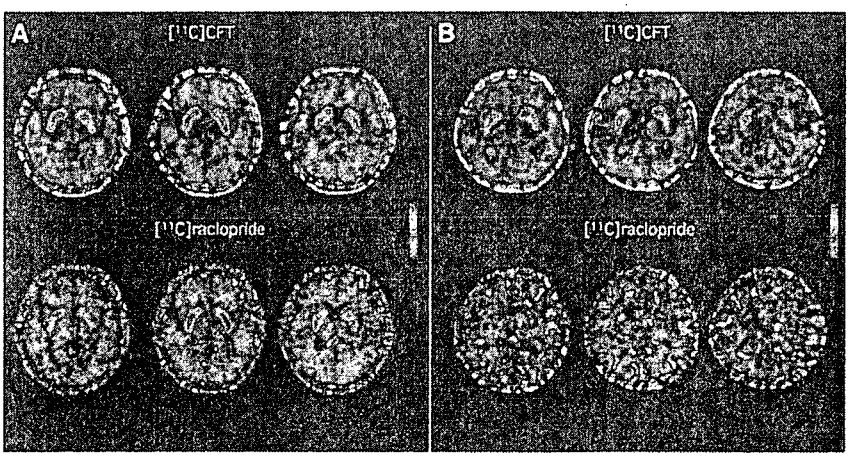

Figure 3 Magnetic resonance imaging–positron emissiontomography fusion parametric images of [^{11}C]CFT and [^{11}C]raclopride binding normalized to the cerebellum in a 68-year-old healthy subject (**A**) and a 77-year-old patient with iNPH (**B**). A marked reduction in [^{11}C]raclopride binding was 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 extrapolate 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

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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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[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).

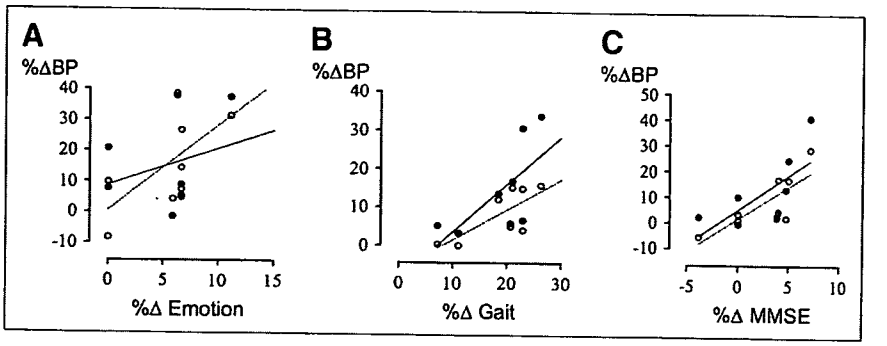

FIGURE 1. Correlations of emotional cognition changes with ^{11}C-raclopride BP changes in nucleus accumbens (A), of navigation time changes with those in dorsal putamen (B), and of MMSE score changes with those in whole striatum (C) on right (○, dotted line) and left (●, solid line) side of brain.

$y = 2.51x + 1.71$, $r^2 = 0.62$; 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

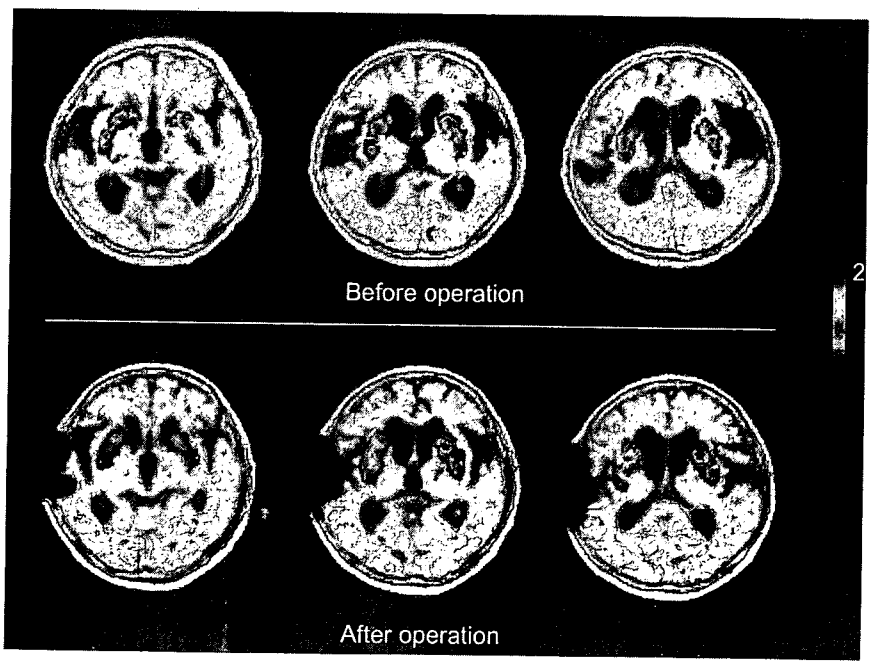

FIGURE 2. PET/MRI fusion parametric images of quantitative ^{11}C-raclopride BP in an iNPH patient before and after shunting. Color bar denotes BP for ^{11}C-raclopride (0–2).

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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MCIについて ——臨床研究におけるMCIの考え方——

鷲見 幸彦

Key words: 軽度認知機能障害、J-COSMIC研究

はじめに

近年認知症をより早期に発見しようという試みが多くなされるようになった。その意義は患者と家族にとっては、認知症は病気であるという意識を確立し、治療により進行抑制や改善する認知症があるという希望を持たせることや、認知症の行動障害に対する対応方法や公的福祉制度の知識を得ることで、介護が容易になり虐待が減ることがあげられる。医師にとっては、早期診断・早期治療を通じて認知症症状の改善や進行抑制、日常生活の指導が可能となり、治療意欲が生じることが考えられ、行政にとっては医療費の削減が可能となり医療経済的効果が期待できることがあげられる。

これらとあいまって、認知症における疫学、画像、神経心理学、バイオマーカーなどの診断技術、治療のあらゆる分野にわたって早期の認知症に対する関心が高まっている。

現在のmild cognitive impairment (MCI)の概念はPetersenらが1995年に提示した概念であるが[1]、その後さまざまな変遷を経ている。本稿ではMCIの概念の変遷と現在の考え方、最近の論文でのMCIの取り扱われ方、認知症の早期診断における脳血流SPECTの有用性を調査する、MCIを対象としたアルツハイマー型認知症の早期診断に関する研究Japan Cooperative SPECT Study on assessment of Mild Impairment of Cognitive function (J-COSMIC)でのMCIの扱い方についてのべる。

I. MCIの概念の変遷と現在の考え方

従来から正常加齢においても、ある程度の認知機能低下は起こりうるという考え方はことに欧州の研究者を中心に存在した。(図1)これらはBSF: Benign senescent forgetfulness[2], AAMI: Age-associated memory impairment[3] ARCD: Age related cognitive decline[4] AACD: Age-associated cognitive decline[5]といった様々な名称で記述されてきた。このうちAACDは加齢に伴う認知機能の低下は記憶障害からのみ始まるものではないとし、言語機能や遂行機能、判断力などの領域から始まることもあるとした点が特記される。この考えは後述する2003年Stockholmでの Consensus Meetingの考え方に大きな影響を与えている。一方米国のPetersenらのグループはあくまで病的過程、主としてアルツハイマー病の前駆段階としてMCIの概念を提唱した。当初彼らはMCIの定義として 1) 自覚的な記憶障害の訴えがある。2) 日常生活動作は正常。3) 全般的認知機能は正常。4) 年齢や教育レベルの影響のみでは説明できない記憶障害が存在し、標準化された記憶検査で平均より1.5 SD以下。5) 認知症ではない。6) CDRのスコアは0.5とした[1]。このMCIの概念への批判がいくつかありその主な論点は 1) この定義のMCIの有病率が約4%と低く。そのうち年間12%が認知症に移行するのでは認知症の年間発症率を説明できない[6]。2) 病理学的な裏づけに欠ける。3) CDR0であっても病理学的にはADの変化を認めることがある。4) 本人の自覚的な記憶障害はあてにならないことなどがあげられた。このうち 2) については病理学的な裏づけとなる論文が出ている[7]。Petersenら自身も1999年[8] 2001年[9]と少しずつMCIの概念を拡大しつつあり、Amnestic type: 健忘型、Multiple cognitive domains slightly impaired type: 複数の高次機能にまたがり軽微な障害があるが全体としては認知症といえないもの、Single non-memory domain impaired type: 記憶以外の高次機能領域であきらかな障害のあるものとMCIをsubtypeに分けている。このうちAmnestic type: 健忘型が従来のMCIに相当する。この健忘型のクライテリアを表1に示した。

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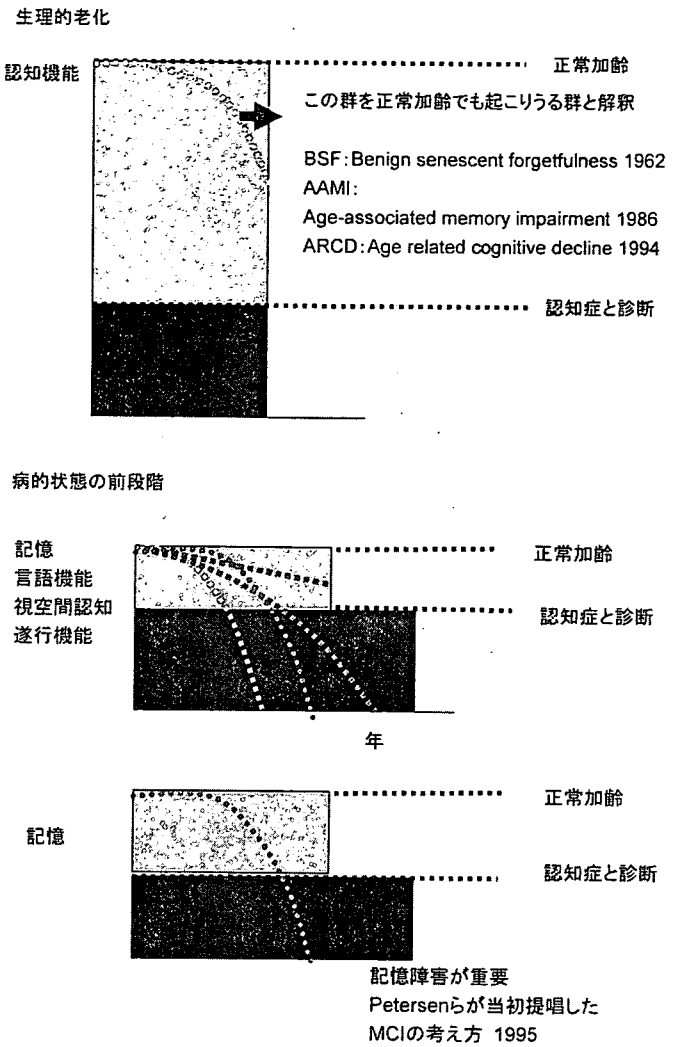

図 1. 軽度認知機能障害の考え方の変遷

表 1. 2001 年 Petersen の amnestic MCI のクライテリア

- 記憶障害の自覚、または情報提供者の証言がある
- 全般的な認知機能は正常
- 日常生活活動は正常
- 認知症ではない
- 記憶障害が年齢を考慮しても客観的に示される

表 2. 2003 Key symposium (Stockholm) での MCI のクライテリア

- 正常ではないが認知症でもない
  (DSM IV, ICD10 の認知症のクライテリアを満たさない)
- 認知機能の低下　自ら　かつ/または　情報提供からの報告があり
  客観的な認知機能検査でも障害が認められること
- 客観的な認知機能検査上、年余にわたる認知機能低下の存在
- 基本的な ADL は保たれており複雑な道具の使用障害が軽度に存在

このような状況のなかで 2003 年 9 月に Sweden の Stockholm で MCI に関する Consensus Meeting が行われ、その内容は 2004 年の Journal of Internal Medicine に掲載された[10]。ここでは MCI の臨床型の heterogeneity とその原因の多様性が強調された。可能性のある原因としては、変性性、血管性、代謝障害、外傷性、精神疾患、その他があげられた。MCI と診断した後には記憶障害が存在するかどうかで 2 群に分かれ、記憶障害のある群ではさらに記憶障害のみなのか他の領域にも認知機能障害があるのかで amnestic MCI と multidomain MCI am-

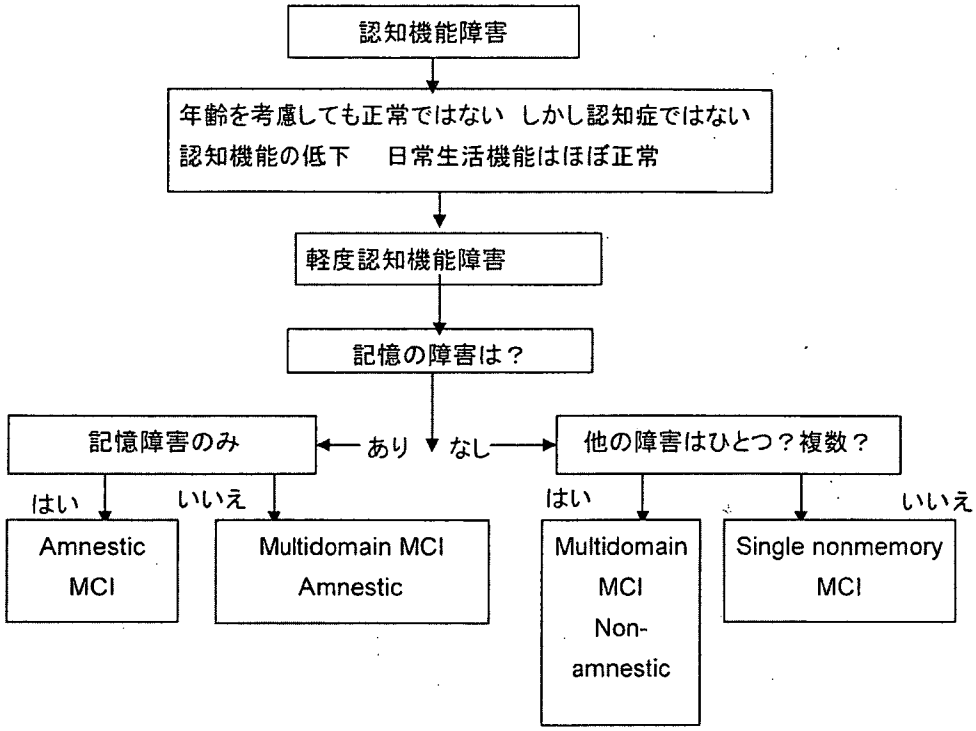

図 2.　MCI の病型分類のプロセス

表 3.　画像関連論文の MCI の具体的な評価基準

著者	雑誌・発表年	内容	具体的な評価基準
Mosconi L et al[11]	Neurology 2005	FDG-PET 海馬の代謝低下	MMSE>24 GDS=3
Rombouts SA et al[12]	Neuroimage 2005	FMRI の BOLD 低下よりも遅延が初期 AD の診断に有用	MMSE>25 CDR 0.5
Johnson NA et al[13]	Neuroradiology 2005	AD　MCI に対する arterial spin-labeling MRI の検討	MMSE 24 以上 CDR 記憶は 0.5 か 1　記憶以外の 2 つ以上の分野が 1 でないことどの分野も 1 を超えない

nestic に分類される。一方記憶障害のない群では障害が単一の領域なのか複数あるかによって、multidomain MCI Non-amnestic と single nonmemory MCI に分類される。(図 2) このシンポジウムにおいてもたとえば記憶障害の検査においてどのバッテリーを用いるのがよいのかといった、具体的な手段についての報告はなかった。MCI の診断基準を考える上で 1) 年齢や教育レベルの影響のみでは説明できない記憶障害の存在これを客観的に示すにはどのような評価尺度がよいのか。2) 正常高齢者との境界をどのように設定するのかといった問題点が残っているように思われる。

II.　最近の論文での MCI の取り扱われ方

それでは最近の論文では実際に MCI をどのような診断基準、あるいはどのような具体的なバッテリーを尺度として用いているのであろうか。2005 年 1-6 月中旬までの MCI の論文数は PubMed で検索すると 194 件にものぼり、そのうち画像に関する論文は 23 件であった。そのうち入手可能な 17 編について検討したところ記載のなかった 3 編を除きいずれも Petersen のクライテリアを使用していた。(2001 年 7 編、1999 年 5 編、1996 年 2 編) 一方具体的な評価方法を示している論文は少なく 6 編のみであり、そのうち 3 編のみが具体的な評価基準まで

記載されていた。(表3) 文献[11-13]少なくとも画像関連の論文では具体的な評価基準が十分記載されていない。

III. J-COSMIC (Japan Cooperative SPECT Study on assessment of Mild Impairment of Cognitive function) 研究における MCI の診断・登録基準

J-COSMIC 研究は長寿科学振興財団の指定研究として 2004 年 (平成 16 年) に開始された。(研究代表者　福井大学米倉義晴)。認知症の早期診断における脳血流 SPECT の有用性を示すエビデンスを提示することを目的に開始された多施設共同研究である。その研究方法は 1) 軽度認知機能障害患者を前向き登録し登録時に 123I-IMP-SPECT を実施する。2) SPECT 診断を行い AD を示唆する画像所見の有無を記載。3) 3 年間の臨床経過観察にて AD 進展例と非進展例を決定。4) 登録時 SPECT の AD 予測診断能を算出する。J-COSMIC における対象は脳血流 SPECT 検査を実施可能な軽度認知機能障害患者である。その選択基準は 1) Amnestic MCI 2) 明らかな神経疾患、精神疾患を認めない。3) 神経学的徴候を認めない。4) 精神医学的徴候を認めない。の 4 点である。amnestic MCI の定義は 2001 年 Petersen らの amnestic MCI のクライテリアを採用した。さらにこのクライテリアに対する操作的な基準として以下のようなツールを用いた。1) 記憶障害の自覚、または情報提供者の証言がある事の裏づけとして数井らが日本語版を作成した生活健忘チェックリストを用いた[14]。2) 全般的な認知機能は正常であることの裏づけとして MMSE が 24 点以上であることとした。3) 日常生活活動は正常であることの裏づけとして CDR を用い、記憶の項目が 0.5 でありかつその他の下位項目はすべて 0.5 以下とした。4) 認知症ではないことの条件として、NINCDS-ADRDA の probableAD の基準を満たさないこととした。5) 記憶障害が年齢を考慮しても客観的に示されるために、WMS-R 論理的記憶 I が 13 点以下という操作的基準を設けた。このように J-COSMIC においては具体的な操作的診断基準を用いたが登録時にはいくつかの問題点が生じた。ひとつは MMSE 日本語版そのものに内在する問題で MMSE の地域差、年齢をどう考慮するかという点である。MMSE では場所の見当識の設問に地方をきく問があるが北海道在住の被験者ではこの質問には答えられないことがある。また高齢者で比較的低学歴の被検者では MMSE 24 点以下でも MCI と考えて問題のない例が存在する。もう一点は WMS-R 論理的記憶 I 14-20 点でも amnesticMCI と診断しておかしくない症例は存在する。70-74 歳の 75% は WMS-R 論理的記憶 I 14 点以上となるため 13 点以下であることを基準としたが、このような症例は今回の研究では対象から外れることとなる。

まとめ

これまでのべてきたように現在 MCI の概念は拡散しつつある。すなわちその初発症状を記憶の障害だけでなく記憶以外の認知機能障害にまで広げていること、単独の病因だけでなく複数の病因を考慮すべきであるという方向に向きつつある。この考え方は確立した概念ではなく今後も流動的であり、変遷していく可能性が高い。そのため MCI を臨床研究の対象とする際には MCI の定義を明確にしておく必要があり、可能な限り操作的な基準を設けて、どのような疾患群を対象にしたのか、具体的にどのような神経心理検査バッテリーを用いたかを明確にしておくことが重要であろう。

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もの忘れ外来における性差

Sex Difference in the Memory Clinic

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Key Words 認知症 (dementia), 性差 (sex difference), もの忘れ外来 (memory clinic)

1．認知症における性差

1）発症率・予後における性差

認知症全体の発症率（incidence）においては多くの報告が女性に高いと報告しており，ことに高齢になるに従って女性の発症率が高くなる[1~3]。仙台におけるMinamiらの報告では65歳以上の地域住民を対象にDSMⅢ-R診断基準として検討した認知症の発症率は，65～69歳で1,000人あたり，男性5.0，女性8.7，70～74歳で男性9.3，女性8.2，75～79歳で男性20.7，女性24.4，80～84歳で男性31.3，女性40.5，85歳以上で男性68.9，女性96.9であった[1]。

オランダにおける検討でも同様の結果が出ている[2]。病型別に検討した報告では，スウェーデンでのデータで，アルツハイマー病（AD）においては75歳以上のあらゆる年齢層で女性の発症率が高く，男性では80～84歳の群のみで発症率が高かった。また血管性認知症（VaD）においては女性であることはリスクとならないことが示された[4]。

清原は久山町のデータをもとに老年期認知症の病型別発症率を検討した。1985年の時点で認知症のなかった827人を1997年まで追跡し，認知症を発症した180例について検討した。その結果，年齢調整後の認知症発症率は，1,000人あたり男性15.6，女性15.9で差はなかったが，病型別の発症率ではADでは男性3.4に対し女性8.3，VaDでは男性9.7に対し女性7.3，その他の認知症では男性2.5，女性1.1であった[5]。

CERAD（The Consortium to Establish a Registry for Alzheimer's Disease）は，米国の21の大学のメディカルセンターがネットワークを形成した多施設のADに関する長期縦断疫学研究であり，その中にADの生存期間について検討した報告がある[6]。1,036人を7年間経過観察し，332人の死亡例があった。平均生存期間は5.9年であったが，男性では5.7年であるのに対し，女性では7.2年であった。男性AD患者における70歳，75歳，80歳の生存期間は6.5年，5.5年，4.4年であり，一般の平均生存期間より明らかに短かった。この結果は人種や教育歴，結婚の有無には関係がなかった。

2）治療における性差

エストロゲンには神経保護作用があることが知られており，認知症の予防効果，および治療効果があるのではないかと期待が持たれた。予防についてはZandiらは前向き研究で閉経後早期にホルモン補充療法を開始した群

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ではADの発症が減少するが，高齢になってからホルモン補充療法を行うとかえって増加すると報告した[7]。Shumakerらは65歳以上の女性を対象に，2,229人のホルモン補充療法群と，2,303人の対照群に対して5年間の前向き研究を行ったところ，ホルモン補充療法群ではADが40人発症したのに対し，対象群では21人の発症で相対危険度は2.05で治療群のほうが高いことを示した[8]。これらの報告からは，エストロゲンを予防的に用いるならば閉経早期の比較的若い時期からの投与が必要となることが示唆されるが，その一方では血栓症の増加や乳癌のリスクを高めるといった別の問題点が浮上してくる。また，どの程度の期間使用すべきかについては，はっきりしておらず，コンプライアンスが保たれにくい。

治療効果については2000年以降無効とする報告が多い。Wangらは25人のAD患者と25人の対照群に結合型エストロゲン1.25mgとプラセボの二重盲検試験を12週間にわたって行い，認知機能および感情障害の検査（CASI, CDR, CIBIC-plus, Behave-AD, Hamilton Anxiety rating scale, Hamilton Depression rating scale）とSPECTによる脳血流の変化を調べたが，認知機能，うつスコア，脳血流のいずれも有意な変化は認められなかった[9]。塩酸ドネペジルについては動物実験でその有効性に性差が存在する可能性が示唆されたが，臨床的には性差の関与は否定的である。RigaudらはApoEのε4対立遺伝子の型や患者の性が塩酸ドネペジル療法に対する反応性の予測因子になるかどうかを，軽中等度のAD患者で検討した。遺伝子の型と性別が，塩酸ドネペジル投与前後のADAS-cog，MMSE，IADL，Clinical global impressionのスコアの差に影響するかどうかを検討したがいずれも有意な差はみられず，性差はドネペジルに対する反応性の予測因子とはならないとしている[10]。

3）介護，その他

カナダにおいてAD患者の介護で，女性の介護者と男性の介護者で介護負担に差があるかどうかを調べた報告がある[11]。在宅の557人の介護者に対して，女性が女性のケアをした場合，女性が男性のケアをした場合，男性が女性のケアをした場合，男性が男性のケアした場合についてその負担度を比較している。その結果，女性が男性をケアした場合に介護負担スケールが5.61高かった。これは，易怒性に代表される精神行動症状が出た際の負担感が大きいためという。

米国においてNursing homeに住むAD患者の性差について解析した報告がある[12]。全体で4万9,607人がADと診断されており，67.9%が女性であった。女性はより高齢で寡婦の傾向がみられ，男性は結婚している例が多

表1　国立長寿医療センターもの忘れ外来の診療科別疾患内訳

	神経内科	精神科	老年科	総数	%
AD	268	212	26	506	58.8
MCI	47	28	7	82	9.5
血管性	26	28	3	57	6.6
DLB	10	6	4	20	2.3
FTD	13	9	1	23	2.7
CBD	5	0	0	5	0.6
PSP	7	0	0	7	0.8
精神疾患	38	5	1	44	5.2
正常	54	3	1	58	6.7
その他	48	5	5	58	6.7
計	516	296	48	860	

い。認知機能そのものには性差はほとんどなかった。男性の入居者はより行動症状を起こしやすく，女性は身体障害を起こしてADLを他人に依存することになる例が多かった。性差による合併症の罹患率には大きな違いがみられ，男性では心疾患，脳血管障害，悪性腫瘍，その他の生命を脅かすような慢性疾患（慢性閉塞性肺疾患やパーキンソン病など）が多い。一方女性では，甲状腺機能低下症や骨粗鬆症や関節炎が多く合併していた。また男性の入居者では，AD special care unitでケアを受ける率が高く，毎日の抗精神病薬の投与，気分，行動，認知機能低下に対する特別なプログラムを受けている率が高い傾向にあることが示された。

2．国立長寿医療センターもの忘れ外来における性差

2000年以降全国に認知症専門外来が増加してきたのは，①AD患者の増加，②核家族化が進み認知症患者を在宅でかかえることが困難になったこと，③認知機能検査，画像診断，バイオマーカーの進歩による早期診断力の向上，④塩酸ドネペジルの発売による早期治療の有用性，などがその背景にあるものと考えられる。

当院においても2001年４月から「もの忘れ外来」として認知症専門外来を開設した。当初は週２回，午後の外来が空いている時間に神経内科医１名と精神科医１名の診療体制で開設したが，現在は月曜から金曜の午後と月曜，火曜，水曜の午前に拡大し，神経内科医４名，精神科医２名，老年科医１名で診療している。2005年３月までに860人の新患を診療し，現在は1,000人を超えている。2005年３月までのもの忘れ外来受診患者の初診時診断を表１に挙げた。約60%がADであり，軽度認知機能障害（MCI）も含めると70%近くがADまたはその前段階であった（表１）。もの忘れ外来の男女比は１：1.8であり，64.3%が女性であった（図１）。

次に主な疾患の性差について検討した。前述のようにADについては女性が，VaDについては男性に多いという報告が多い。レビー小体型認知症（DLB）については男性に多いという報告が多く，1.5：１から３：１という報告がある[13]。ADについては男性164例，女性342例であり受診者数で補正すると0.85：１で女性に多かった。MCIでは男性25例，女性57例であり0.8：１である。VaDは男性31例，女性26例であり，２：１と男性に多

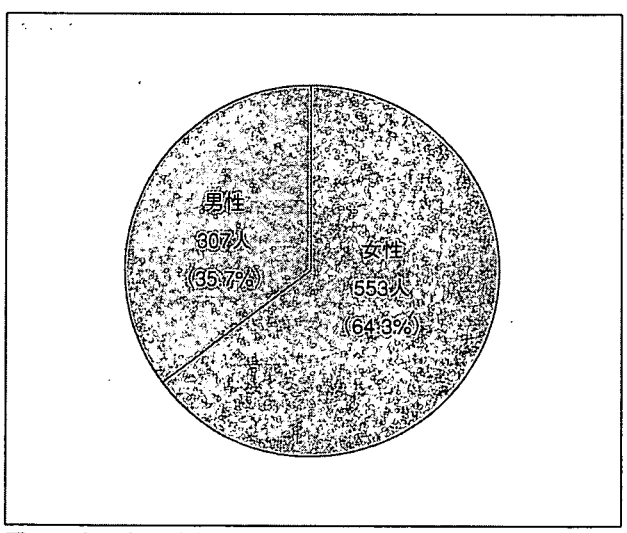

図１　もの忘れ外来の男女比

表２　当院もの忘れ外来における主要疾患の男女比

	総数	男性	女性	男女比
AD	506	164 / 307	342 / 553	0.85 : 1
MCI	82	25 / 307	57 / 553	0.8 : 1
VaD	57	31 / 307	26 / 553	2 : 1
DLB	20	10 / 307	10 / 553	1.5 : 1
FTD	23	13 / 307	10 / 553	2 : 1

AD : Alzheimer disease　　DLB : Lewy body dementia
MCI : Mild cognitive impairment　　FTD : Fronto temporal dementia
VaD : Vascular dementia

い。DLBは男性10例，女性10例であり，1.5：1で男性に多く，前頭側頭型認知症（FTD）は13例と10例で2：1と男性に多かった（表2）。これらの結果は，ADとその前段階が多いと考えられるMCIでは女性に多く，血管性の認知症やその他の変性性認知症では男性に多いという従来の報告と合致した結果であった。

3．まとめ

もの忘れ外来では「もの忘れ」記憶障害を主訴に受診することが多いためにADの頻度が高い。このようなやや特殊な条件下ではあるが，性差に関しては一般の認知症の特徴が同様に発現している。認知症の治療法やケアについての性差は重要な問題であり，ことにケアについての性差は重要であるが，意外に意識されていない。今後この面での大規模な検討が必要であろう。

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