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Decreased Benzodiazepine Receptor Binding in Machado-Joseph Disease

Masatoshi Ishibashi, Tetsuo Sakai, Toyojiro Matsuishi, Yoshiharu Yonekura, Yushiro Yamashita, Toshi Abe, Yoshihiro Ohnishi and Naofumi Hayabuchi

Division of Nuclear Medicine and Department of Radiology, Department of Pediatrics and Child Health, Kurume University School of Medicine, Kurume-City; Department of Neurology, National Chikugo Hospital, Fukuoka; Biomedical Imaging Research Center, Fukui Medical School, Fukui; and Nihon Medi-Physics Co., Ltd., Hyogo, Japan

Benzodiazepine receptor binding was assessed in four Japanese men with Machado-Joseph disease. **Methods:** The distribution of benzodiazepine receptors was measured by radionuclide imaging (SPECT) after intravenous administration of ^{123}I-iomazenil (Ro 16-0154). **Results:** SPECT demonstrated decreased binding throughout the cerebral cortex and cerebellum in all patients. Binding potential (receptor concentration × affinity) was diffusely decreased in cerebral cortex, thalamus, striatum and cerebellum compared with control subjects, suggesting that GABAergic function may be decreased globally in these patients. Cerebral blood flow was largely normal, and no cerebral cortical atrophy was evident on MRI. **Conclusion:** Iodine-123-iomazenil SPECT may become a potent method for detecting impairment of the cerebral cortex even before brain perfusion SPECT or MRI can reveal early abnormalities.

Key Words: iodine-123-iomazenil; benzodiazepine receptor; Machado-Joseph disease; SPECT

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Machado-Joseph disease (MJD) is an autosomal dominant neurodegenerative disorder that was originally described in patients of Portuguese-Azorean ancestry (*1*). Cytidylate, adenylate and guanylate (CAG) expansions in a novel gene at chromosome 14q 32.1 have been discovered in Japanese patients with MJD (*2*). However, the mechanism of central nervous system impairment in such patients is still unknown.

Brain function can be delineated by coupling morphology and receptor imaging (*3*). Imaging of gamma-aminobutyric acid (GABA)/benzodiazepine receptors may help to determine whether GABAergic transmission is impaired in patients with MJD, because the basal ganglia and cerebellum show degeneration in such patients. Iomazenil (Ro 16-0154) is an agonist of benzodiazepine with a high affinity for the central type of benzodiazepine receptor (*4*). This agent can be labeled with ^{123}I without losing binding properties (*5*). Early ^{123}I-iomazenil images primarily reflect blood flow, whereas delayed images taken 3 hr after injection of tracer reflect benzodiazepine receptor binding (*5*).

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For correspondence or reprints contact: Masatoshi Ishibashi, MD, Department of Radiology and Division of Nuclear Medicine, Kurume University School of Medicine, 67 Asahi-Machi, Kurume City, Fukuoka, 830-0011, Japan.

MATERIALS AND METHODS

Study Population

Four Japanese men with MJD (age range 34–57 yr, mean 44 yr) were examined (*6*). The diagnosis was confirmed by identification of CAG expansions (*2*). Data from the four patients were compared with those from six healthy age-matched control subjects (age range 24–61 yr, mean 39.7 yr) (*7*). These control subjects gave informed consent.

All four patients with MJD gave informed consent as part of a protocol approved by the Subcommittee on Human Studies at Kurume University School of Medicine. The clinical features of the patients are summarized in Table 1. No benzodiazepine derivatives were administered.

Data Acquisition and SPECT

The labeled receptor ligand ^{123}I-iomazenil was obtained from Nihon Medi-Physics Co. (Nishinomiya, Japan). A bolus of 167 MBq ^{123}I-iomazenil was injected intravenously. SPECT was performed 20 min (early image) and again 3 hr (delayed image) after injection of tracer using a large-field-of-view, dual-detector camera (RC26001; Hitachi, Tokyo, Japan) and a computer system (RW3000; Hitachi) equipped with a low-energy, high-resolution, parallel-hole collimator. The dual-detector camera was rotated over 180° in a circular orbit and in 32 steps of 40 sec each to cover 360° in approximately 22 min. Coronal and sagittal images were derived from the transaxial images. Venous blood samples were drawn 30 min after the radiotracer injection. Ligand-receptor binding was assessed by determining binding potential (Bp), which is defined as a product of the receptor concentration (Bmax) in the brain tissue and the ligand-receptor affinity (1/kD) (*8*). Bp was obtained in the manner reported previously (*9*) for regions of interest corresponding to frontal, occipital, temporal and parietal cortices; thalamus; striatum; and cerebellum. Individual arterial input function was estimated by scaling a standardized shape of time-concentration curve input function and two separate SPECT scans (20 min and 3 hr postinjection) using a table lookup procedure based on a three-compartment, two-parameter kinetic model.

Cerebral blood flow (CBF) images were obtained 20 min after the intravenous injection of 222 MBq ^{123}I-N-isopropyl-p-iodoamphetamine (IMP) using the same equipment and data processing as those for ^{123}I-iomazenil images.

TABLE 1
Clinical Features and Imaging Results in Four Men with Machado-Joseph Disease

Clinical Features and Imaging Results				
Patient no.	1	2	3	4
Age (yr)	57	34	43	40
Age at onset (yr)	44	16	36	30
Duration (yr)	13	18	7	10
CAG expansion	+	+	+	+
Symptoms and signs				
Cerebellar ataxia	++	–	–	+
Pyramidal signs	+	++	++	+
Extrapyramidal signs	±	++	–	+
Amyotrophy	–	++	–	–
IMP SPECT	Hypoperfusion (Ce, Lt T)	Normal CBF	Hypoperfusion (Lt T)	Normal CBF
Iomazenil SPECT				
Early	Normal	Normal	Moderate decrease (Lt T)	Normal
Delayed	Diffuse decrease	Decrease	Diffuse decrease	Diffuse decrease
	Grade 2	Grade 4	Grade 3	Grade 3
MRI	Cerebellar atrophy	Cerebellar atrophy	Normal	Cerebellar atrophy

CAG = cytidylate, adenylate and guanylate; CBF = cerebral blood flow; Ce = cerebellum; F = frontal; IMP = ^{123}I-N-isopropyl-p-iodoamphetamine; Lt = left; T = temporal.

Evaluation of Iomazenil SPECT

Late iomazenil SPECT images (3 hr postinjection) were evaluated by both visual analysis and quantitative analysis of Bp. In visual analysis, the SPECT images were interpreted by consensus among three observers blinded to the clinical information. A four-point scale was applied: Grade 1, normal; Grade 2, slight decrease; Grade 3, moderate decrease; and Grade 4, severe decrease. Disagreements were resolved by consensus.

MRI

All patients underwent MRI within 1 wk before ^{123}I-iomazenil SPECT. MR images were acquired on a superconducting magnet operating at 1.5 T (Magnex 150HP; Shimadzu, Kyoto, Japan). Imaging parameters consisted of conventional spin-echo sequences (580/20 msec) for T1-weighted images and (6000/88 msec) for T2-weighted images; 5-mm section thickness, with 1-mm interslice gap; and 512 × 512 acquisition matrix.

RESULTS

Table 1 shows the clinical features of patients and the results of MRI, IMP SPECT and ^{123}I-iomazenil SPECT, including grade classification. Iodine-123-iomazenil SPECT study in a control subject is shown in Figure 1. Visual analysis demonstrated reduced iomazenil binding in delayed SPECT images in various regions examined in all patients compared with normal subjects, whereas IMP SPECT images showed a normal CBF pattern except for moderate hypoperfusion of the cerebellum and left temporal cortex in Patient 1 and moderate hypoperfusion of left temporal cortex in Patient 3.

MRI showed cerebellar atrophy in three patients with MJD. Figure 2 shows the results of Bp obtained by ^{123}I-iomazenil SPECT in patients and normal subjects. Bp was diffusely decreased throughout the cerebral cortex and thalamus, as well as throughout the cerebellum and striatum ($p < 0.001$). Representative ^{123}I-iomazenil SPECT, ^{123}I-IMP SPECT and MR images of a patient with MJD (Patient 2) are shown in Figure 3.

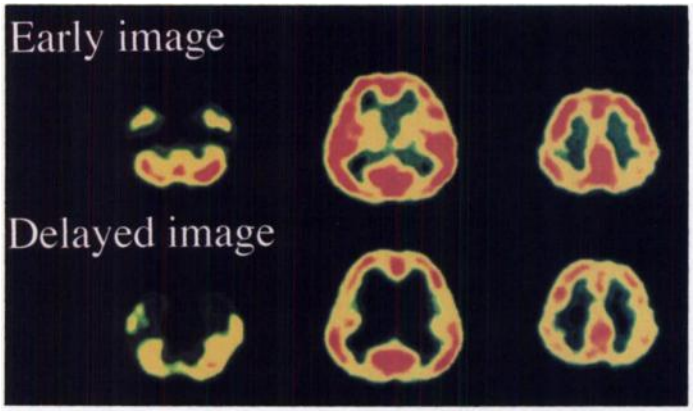

FIGURE 1. Early and delayed ^{123}I-iomazenil SPECT images show changes in a control subject.

DISCUSSION

This study was conducted to determine whether GABAergic or benzodiazepine receptor-mediated transmission may be involved in patients with MJD, since the GABAergic system is

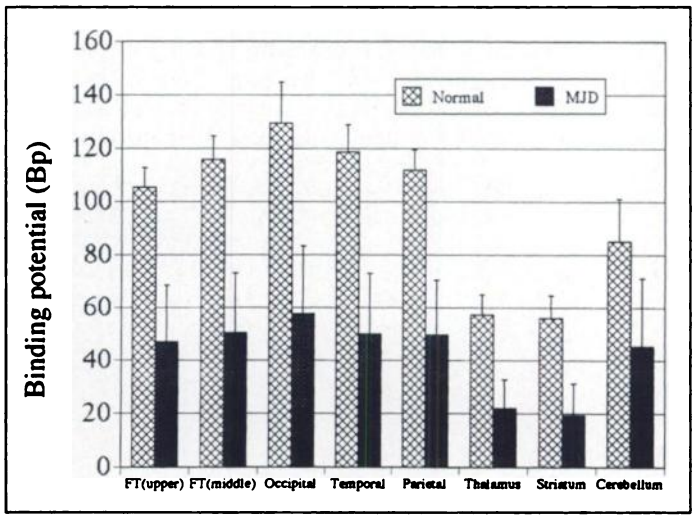

FIGURE 2. Binding potential of ^{123}I-iomazenil SPECT in patients (dark shaded column) and control subjects (cross-hatched column). Differences in Bp were evident ($p < 0.001$) in all regions between MJD patients and control subjects. FT = frontal.

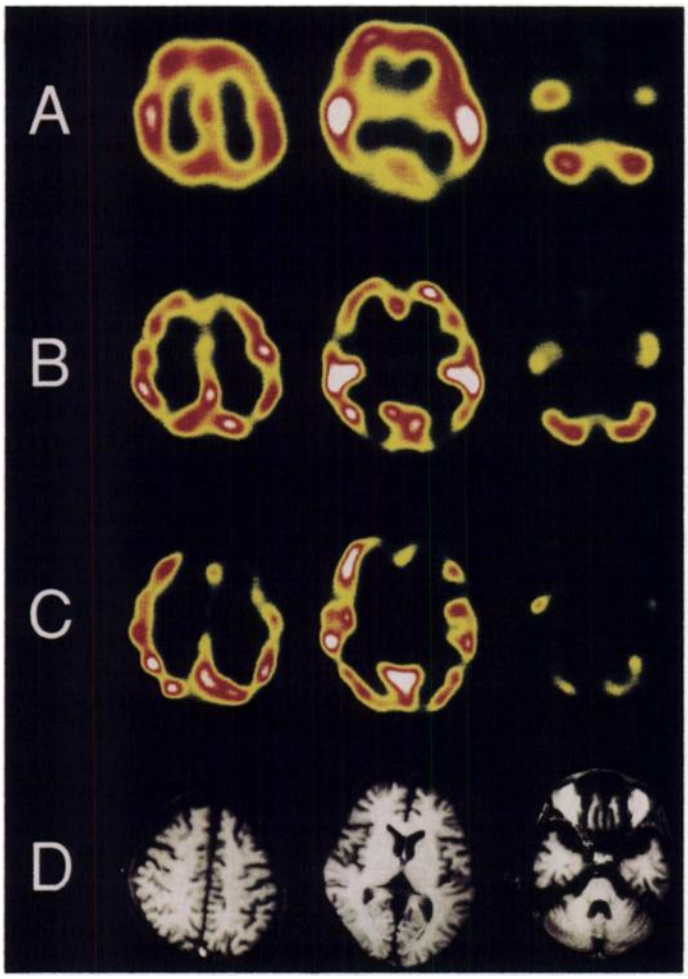

FIGURE 3. Typical brain images of a patient with MJD (Patient 2). (A) ^{123}I-IMP SPECT image demonstrates normal CBF. (B) Early ^{123}I-iomazenil SPECT image demonstrates normal uptake. (C) Delayed ^{123}I-iomazenil SPECT image shows marked reduction in benzodiazepine binding in bifrontal cortex and moderate reduction in binding in cerebellum. Binding potential was markedly decreased in these and other seemingly normal regions. (D) T1-weighted MR images show mild cerebellar atrophy.

important in cerebellar and extrapyramidal function. In this study, delayed ^{123}I-iomazenil SPECT images revealed varying but significant global decreases in benzodiazepine receptor binding not only in the cerebellum and the striatum but also in the cerebral cortices and the thalamus in patients with MJD.

We had speculated that ^{123}I-iomazenil imaging would demonstrate some abnormalities in the cerebellum or striatum, where degeneration has been reported in patients with MJD (*1*). Unexpectedly, we also found a decrease of benzodiazepine receptor binding in the cerebral cortex and the thalamus. Previous neuropathologic reviews have not revealed abnormalities in the cerebral cortex (*1,10*), and the reason for such an extensive decrease in benzodiazepine receptor binding is not immediately understood. However, Taniwaki et al. (*11*) recently reported that with ^{18}F-fluoro-2-deoxy-D-glucose PET, regional cerebral glucose metabolism in MJD was significantly decreased throughout the cerebral cortex, as well as throughout the cerebellum and striatum. The report speculated that such a decrease might reflect the effect of deafferentation from lower structures such as the cerebellum, basal ganglia and brain stem. Such an explanation also may apply to the decrease of benzodiazepine receptor binding in the cerebral cortices in MJD.

In conclusion, ^{123}I-iomazenil SPECT is a sensitive method for detecting early diminution of GABAergic function in patients with MJD.

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