A 50-year-old woman presented with progressive visual disturbance, ataxia, and dementia. The cerebral cortex became atrophic, as the disease progressed, and electroencephalography showed periodic synchronous discharges. The patient’s prion gene revealed a point mutation (232Met to Arg), and a diagnosis of Creutzfeldt-Jakob disease was made. Iomazenil single-photon emission computed tomography (SPECT) was performed to assess neuronal degeneration. Accumulation of the tracer in the late images was severely decreased diffusely spread throughout the cerebral cortex. Our experience with this case suggests that iomazenil SPECT is useful for detecting neuronal degeneration in Creutzfeldt-Jakob disease.

Key words: iomazenil, receptor imaging, dementia, prion disease

Introduction

Creutzfeldt-Jakob disease (CJD) is a distinct disease entity characterized by subacutely progressive dementia, myoclonus, and cerebellar ataxia, together with periodic synchronous discharges on electroencephalograms (EEG) (1–3). Pathologically, diffuse cerebral atrophy becomes evident as the disease progresses. Microscopic findings include neuronal loss, astrocitosis, and the development of cytoplasmic vacuoles in neurons and astrocytes (status spongiosis). The cortex and basal ganglia are most severely affected. A single-photon emission computed tomography (SPECT) method using a ligand for benzodiazepine receptors was recently developed and found to be effective in detecting neuronal degeneration. Here, we report the SPECT findings in a patient with CJD, and suggest the usefulness of the examination for evaluating this disease.

Case Report

A 50-year-old woman, a French interpreter, was admitted to our hospital complaining of visual disturbance and unbalanced gait in July 1993. She was born of healthy, nonconsanguineous parents with no family history of neuromuscular disease. The delivery, and the patient’s physical and mental development had been normal. The patient had given birth to two healthy children. In January 1993, she first noticed mild difficulty in focusing her vision. In March, she realized that her translation from French to Japanese had become slower and she often had difficulty recalling some French words during her translation work. Her gait became ataxic in June, and her memory deteriorated.

On admission, the neurological examination revealed alert consciousness, but she responded very slowly and with some incorrect words. She was moderately disoriented and had difficulty recalling general information. Repetition of two digits both forward and backward was impossible. No points were obtained on Kohs’ Cubic Combination Test, and the patient could not perform Wechsler Adult Intelligence Scale (WAIS) test because of inability to concentrate. The score on a memory test assessed by pairing words was 5 points out of 10 for related words and 0 points out of 10 for unrelated words. Cranial nerve testing was negative and muscle strength was normal. No abnormalities were found in tendon reflexes or the sensory system. Coordination tests showed severe dysdiadochokinesias, especially on the left, and the finger-nose-finger test revealed mild dysmetria on the left. The heel-to-shin test was abnormal bilaterally, and truncal ataxia was noted. The patient’s gait was ataxic, and tandem gait was impossible.

In the laboratory studies, urinalysis, fecal occult blood test, erythrocyte sedimentation rate, blood counts, and blood coagu-
Benzodiazepine Receptor Imaging in CJD

SPECT was performed in March 1994 using 123I-iomazenil (IMZ) as a tracer to detect benzodiazepine receptors in the central nervous system. This tracer was allowed to use as a clinical trial targeting patients with dementia and cerebrovascular disease. The trial was approved by the Institutional Human Investigation Committee of Keio University. All patients gave their informed written consent. Their families substituted for those who could not write with their own hand or who could not understand the purport in a case like this. A diagnosis of CJD was made.

After admission to the hospital, the patient's gait disturbance and dementia progressed. She became unable to walk in August and spoke only a few jargons. She stopped eating in the middle of August, and tube feeding was started. Myoclonus was observed in the next few months, and an EEG showed periodic synchronous discharges. The patient exhibited akinetic mutism in October. A CT scan showed cortical atrophy in January 1994 (Fig. 1D). The myoclonus gradually disappeared in March 1994.

SPECT was performed in March 1994 using 123I-iomazenil (IMZ) as a tracer to detect benzodiazepine receptors in the central nervous system. This tracer was allowed to use as a clinical trial targeting patients with dementia and cerebrovascular disease. The trial was approved by the Institutional Human Investigation Committee of Keio University. All patients gave their informed written consent. Their families substituted for those who could not write with their own hand or who could not understand the purport in a case like this. A 110 MBq dose of ligand was bolus injected intravenously, and scanning was performed 15 and 180 minutes after the injection as early and late images, respectively, using a triple-headed rotatory gamma camera (Toshiba GCA9300A/HG, Tokyo). The images were reconstructed by a filtered-back projection method, preprocessed through a Butter-Worth type of filter and then processed through a two-dimensional filter for smoothing. As for absorption correction, precorrection following Sorenson's method was performed. The early image, which is known to correspond to cerebral blood flow (CBF), showed mild hypoperfusion diffusely spread in the cerebral cortex (Fig. 1A). The decrease was definite in comparison with the cerebellum. It is more noticeable that the accumulation of IMZ in the late image was severely decreased and diffusely spread in the cerebral cortex (Fig. 1B). In general, late IMZ SPECT images are known to reflect the density of benzodiazepine receptors in the central nervous system so that reduced accumulation of the ligand indicates neuronal loss or degeneration. Thus, the diffuse reduction of ligand accumulation in the late images in this patient appeared to reflect neuronal degeneration caused by CJD. Two weeks before the iomazenil scan, SPECT was performed with 99mTc-HMPAO to measure CBF (Fig. 1C). Decreased accumulation was noted diffusely throughout the cerebral cortex, but the extent was moderate and consistent with the early iomazenil SPECT images.

Since no control IMZ SPECT data in normal volunteers is available, SPECT images of three patients with lacunar infarction (2 male cases and 1 female) were utilized for comparison. The use of IMZ was also approved as part of the trial described above. An early IMZ SPECT image in a patient with lacunar infarction is shown in Fig. 1E. This image is reported to mainly reflect CBF, and no decrease in ligand accumulation was observed, suggesting grossly normal blood flow. Figure 1F shows the late image in the same patient with lacunar infarction. The accumulation of ligand was mainly observed in the cerebral cortex, with much less tracer accumulation in the cerebellum. This pattern of accumulation is considered normal. Comparison of the late IMZ SPECT images in CJD (Fig. 1B) and lacunar infarction (Fig. 1F) clearly shows the extreme reduction in IMZ accumulation in the cerebral cortex in CJD. MRI findings in the lacunar infarction case are shown in Fig. 1G. Several lacunae are observed in the basal ganglia and deep white matter.

To evaluate the reduction in the tracer accumulation semiquantitatively, regions of interest (ROI) were positioned on the frontal, parietal, temporal, and occipital cortex and cerebellum on both sides, or only on one side if the lacunae were within or close to the ROI. The ratios of the averaged counts within each ROI to that of the cerebellum were calculated. Figure 2 shows the relative ligand accumulation in each ROI in the CJD patient and lacunar infarct patients. In the early scans, accumulation in the CJD case was lower than in the lacunar infarction cases in all areas of the cortex. The averaged count of all ROI in CJD was 85.1% compared to 110.7 ± 11.7% (mean ± SD) in the lacunar infarct cases. In the late images, there was even less ligand accumulation in all ROI's in CJD, whereas it was increased in the lacunar infarct cases. The average count of all ROI's was 47.9% in the CJD case, as opposed to 128.7 ± 7.2% in the lacunar infarct cases. It is noteworthy that the gap in accumulation between the CJD case and the lacunar cases became more pronounced in the late image, suggesting that the neuronal degeneration was diffuse in CJD. Although the IMZ SPECT in the present case was performed in the advanced stage of CJD, presumably IMZ SPECT can detect neuronal degeneration even in earlier stages.

Discussion

SPECT has recently been adapted not only to measure CBF but to detect the density of certain receptors on neurons, and 123I-iomazenil is now being used clinically to detect benzodiazepine receptors (5–8). The early image reflects CBF, while the late image is known to closely parallel the binding capacity of benzodiazepine receptors. In general, benzodiazepine binds to two types of binding sites, central receptors and peripheral acceptors. Iomazenil binds specifically to the central type of benzodiazepine receptors, which are located only on
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Figure 1. (a) Early iomazenil SPECT images of the present case. Diffusely reduced accumulation in the cerebral cortex is observed, compared with accumulation in the cerebellum and basal ganglia. (b) Late iomazenil SPECT images in the present case. Severely reduced accumulation of the tracer is observed in the cerebral cortex, but it is maintained in the cerebellum. (c) HMPAO SPECT in the present case. Diffuse hypoperfusion is apparent in the cortex, while cerebral blood flow is maintained in the basal ganglia and cerebellum. The pattern is consistent with that of the early IMZ SPECT image. (d) CT in the present case two months before IMZ SPECT. Cortical atrophy can be seen. (e) Early iomazenil SPECT image in a patient with lacunar infarction. Accumulation in the cerebral cortex is relatively well maintained in comparison to the basal ganglia and cerebellum. (f) Late iomazenil SPECT images of the same patient with lacunar infarction. Cortical accumulation is even higher than in the cerebellum. (g) MRI images of the same patient with lacunar infarction.
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![Image of cortical accumulation of iomazenil in a patient with Creutzfeldt-Jakob disease (CJD) and in three patients with lacunar infarction. Relative accumulation has been calculated in each part of the cortex as a percentage of accumulation in the cerebellum in the same scan. Judging from the early images, cerebral blood flow is considered to be decreased in CJD compared to the patients with lacunar infarction. More noticeably, accumulation of the ligand in the late image is severely decreased in CJD, but maintained in lacunar infarction.](image)

Figure 2. Cortical accumulation of iomazenil in a patient with Creutzfeldt-Jakob disease (CJD) and in three patients with lacunar infarction. Relative accumulation has been calculated in each part of the cortex as a percentage of accumulation in the cerebellum in the same scan. Judging from the early images, cerebral blood flow is considered to be decreased in CJD compared to the patients with lacunar infarction. More noticeably, accumulation of the ligand in the late image is severely decreased in CJD, but maintained in lacunar infarction.

neurons. Thus the late SPECT images had been suggested to be useful in detecting neuronal degeneration in the cortex. Patients with temporal lobe epilepsy, Alzheimer's disease, cerebral infarction, and spino-cerebellar degeneration were examined and found to have abnormal distribution of benzodiazepine receptors (5-8). The present study showed decreased cortical benzodiazepine receptor binding in a patient with CJD for the first time, suggesting diffuse neuronal loss in the cerebral cortex. No positron emission tomography (PET) study using a ligand for benzodiazepine, such as flumazenil, has ever been conducted to detect neuronal degeneration in CJD.

Interestingly, Aguglia et al (9) reported that benzodiazepine receptors of the primary somatosensory cortex were preserved in a specific phase of CJD. They employed evoked potential and investigated the effects of various drugs. Diazepam decreased the amplitude of evoked potential and it was reversed by flumazenil. They emphasized the preservation of benzodiazepine receptors, however they did not compare it with a normal control. Indeed, in the present study also, the accumulation of tracer was detected, though the amount was remarkably decreased.

Myoclonus is a typical sign of CJD and is related to abnormal excitability of neurons. However, GABA receptors and benzodiazepine receptors are known to make a single complex. The degeneration of these inhibitory systems might be an underlying factor in the occurrence of myoclonus in CJD. Quite often, the loss of neurons is detected chemically and pathologically before the onset of symptoms. Thus, there is a possibility that the SPECT image using IMZ may detect the decrease of benzodiazepine receptors in the early stage of the disease even before the myoclonus appears.

As the disease progresses, the cerebral cortex becomes diffusely atrophic, and the apparent accumulation of any isotope ligand seems reduced due to the reduction in accumulated volume. However in the present case, accumulation of the ligand in the late images was much lower than in the early images, and the gap was visually apparent. The absolute amount of accumulation was not suitable for comparison, but accumulation in the cerebellum can be used as a standard and relative amounts can be compared in different cases. Quantitative comparison of relative IMZ accumulation in the CJD case and the lacunar infarct cases more clearly revealed that reduction in ligand accumulation is much heavier in the late images than in the early images in the CJD patient. Thus the effect of the atrophy on the apparent decrease of the ligand accumulation in the late image can be neglected in the present case.

Also, there is a possibility that the absolute accumulation of IMZ in the cerebellum in the CJD case might be reduced from normal, reflecting the possible neuronal degeneration in the cerebellum. However that would only underestimate the relative accumulation of the other ROI in comparison to that of the cerebellum, because the ratio will be smaller when ROI is compared with a larger number. In the CJD case, the decrease of IMZ accumulation was remarkable even when the ratio to the cerebellum was adopted for the comparison. The factor of difference in the cerebellar accumulation did not affect the
In the present case, IMZ SPECT was performed when the disease was well advanced. The diagnosis had already been made based on the clinical findings and laboratory studies including an EEG and CT. Since IMZ SPECT is thought to detect neuronal degeneration, it might be useful for early diagnosis of the disease before the atrophy appears. Recently SPECT images have been reported to detect reduced CBF even in the early stage of the CJD (10). However, since the CBF changes in this disease are secondary to the neuronal degeneration, the SPECT with iomazenil is expected to be more sensitive. Further studies in the early stage of CJD are warranted.

In conclusion, our experience in this case suggests the SPECT images produced with iomazenil are useful in detecting neuronal degeneration in the cerebral cortex in CJD patients. Further evaluation is needed to establish the validity of this SPECT technique for diagnosing CJD in the early stage before cerebral atrophy occurs.

References