Dopamine Transporter SPECT of a Liver Cirrhotic with Atypical Parkinsonism

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Abstract: High level of exposure to manganese (Mn) can cause a clinically and pathophysiologically distinct syndrome from idiopathic Parkinson's disease (PD). We describe the clinical features and results of [^{123}I]-fluoropropyl (FP)-CIT SPECT of a liver cirrhotic with atypical parkinsonism. The patient developed atypical parkinsonian features associated with elevated blood Mn from hepatic dysfunction. [^{123}I]-FP-CIT brain SPECT images of dopamine transporter (DAT) demonstrated overall normal range of DAT uptake in the striatum although there were scattered small hypodense regions. The globus pallidum had increased signal on T1-weighted magnetic resonance imaging (MRI). All these findings are compatible with those of manganism, and are remarkably different from that in PD.

Key words: Manganism, Liver cirrhosis, SPECT, Dopamine transporter, Parkinson's disease

Introduction

Recently, liver cirrhosis-related parkinsonism have been the subject of interest[1–18]. Burkhard *et al*. described a series of chronic parkinsonism associated with liver cirrhosis comprehensively[17]. The authors described the clinical characteristics of chronic parkinsonism associated with liver cirrhosis as follows: rapidly evolving and symmetric akinetic-rigid syndrome, early gait and postural impairment and focal dystonia. Resting tremor is notably minimal or absent, but postural tremor is prominent. Cognitive functions are globally preserved. Thus, the authors indicated that their clinical characteristics were different from those of Parkinson's disease (PD). Klos *et al*. also described neurologic spectrum of chronic

liver failure, and parkinsonism syndrome as one of the neurologic spectrum[18]. The authors also indicated several distinctive clinical differences in comparison with PD although some of them demonstrated clinical improvement with L-dopa. However, the study with fluorodopa positron emission tomography (PET) or dopamine transporter (DAT) single-photon emission computed tomography (SPECT) on cirrhosis-related parkinsonism is very rare to our knowledge[19]. We report a liver cirrhosis case with atypical parkinsonism whose DAT SPECT finding is remarkably different from that in PD and that in Racette *et al*.[19].

Case Report

Clinical and occupational history

This 42-yr-old man had a 12-yr history of hepatitis B related

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liver cirrhosis. Hepatitis B related liver cirrhosis was diagnosed using past medical history combined with clinical, laboratory, endoscopic, ultrasonographic and computed tomography (CT) findings. He had grade IV of esophageal varices and portal hypertension. He have had several episodes of hepatic encephalopathy which was improved by correction of precipitating factor such as infection and constipation. He first began to experience gait instability at age 41. He began to drag his feet and have frequent falls. He had facial bone fracture and subdural hematoma because he had severe postural instability and gait impairment with frequent fall-down. Within a few months, he was unable to independently rise from bed and needed assistance to walk. Within the first 7 months, he became depressive and emotionally labile with excessive tearfulness precipitated by minor emotional stressors.

He had been an office worker until retirement due to liver cirrhosis. An extensive environmental and occupational history failed to detect an external source of Mn. Medication history was denied except liver disease.

A dose of benserazide/L-Dopa (150 mg/d) was started 20 months after symptom onset, and increased to 750 mg/d of benserazide/L-Dopa. But he did not show any improvement of symptoms and signs during 1 yr of follow-up.

Clinical examination findings

On the physical examination, 18 months after symptom onset, abdomen was distended and pitting edema was noted on the both lower extremities. On neurological examination, he showed prominent symmetric rigidity, bradykinesia, postural tremor, and gait disturbance. He walked slowly with short shuffling steps, stooped posture, reduced arm swing, and freezing episode. Turning around was difficult and the pull-test result was positive. The motor function score (part III) of the Unified Parkinson Disease Rating Scale (UPDRS) was 23/56 and Hoehn and Yahr stage was 4.

Laboratory and imaging findings

Whole blood manganese (Mn) was 2.4 μg/dl (reference range, <2 μg/dl). Serum albumin was 2.2 g/dl (reference range, 3.5–5 g/dl). Prothrombin time (22.6 s; reference range, 11–14 s) was prolonged and total bilirubin (3.4 mg/dl; reference range, 0.1–1.2 mg/dl) was elevated. Serum copper and ceruloplasmin were normal. Magnetic resonance imaging (MRI) examinations were performed using a 1.5 Tesla system (Signa Horizon LX; GE Medical Systems; Milwaukee, WI). MRI showed symmetrical high signal intensities in the globus pallidus on T1-weighted images (Fig. 1).

[123I]-FP-CIT SPECT images was performed using a dual headed gamma camera (ADAC Forte, Philips Medical
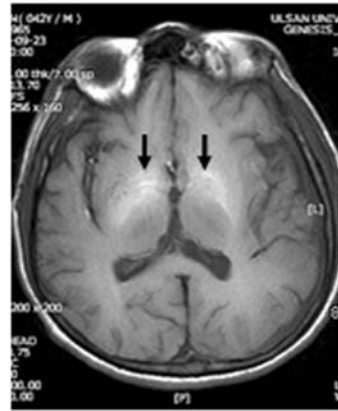

Fig. 1.   Axial section showed symmetrical high signal intensities in the globus pallidus on T1-weighted magnetic resonance images (MRI) (arrows).

System) equipped with parallel-hole, low-energy, high resolution collimators. SPECT data acquisition was started 4 h after intravenous injection of 185 MBq of [123I]-FP-CIT (DATScan; Amersham GE Healthcare). Total 120 projections were acquired over 360° using step-and-shoot mode and a 128 × 128 matrix was used. Projection data were checked visually for the patients' motion during the scanning by cine display and sonogram. Image reconstruction was performed using filtered back projection filtered with Butterworth filter (cutoff frequency; 0.3 cycle/cm, 10th order). Attenuation was corrected using Chang's method (attenuation coefficient: 0.12 cm^{-1}). The regions of interest (ROIs) for the caudate, putamen and the striatum as a whole were determined and the mean radioactivity in the ROIs and the occipital cortex serving as a reference region were measured. The specific radiotracer binding for DAT was calculated as the ratio of radioactivity in the ROIs and occipital cortex (binding potential = ROIs /occipital cortex -1). The SPECT data from healthy control subjects and patients with PD from our database were collected and analyzed with same method for comparison.

Figure 2 shows [123I]-FP-CIT brain SPECT images of DAT taken from the patient (A), a healthy control (B) and a PD (C). The color bar presents the binding potential (BP) calculated as the ratio of region to occipital uptake. In the patient (A), the overall DAT in the striatum shows in normal range (BP: 3.19 (left), 3.20 (right)) as compared with that in healthy control subjects (mean BP in the striatum: 3.20 ± 0.49, n=12). However, the radiotracer in the putamen showed a mild decrease with scattered small hypodense regions. In a patient with PD (C), a significant reduction of DAT in the putamen was observed.
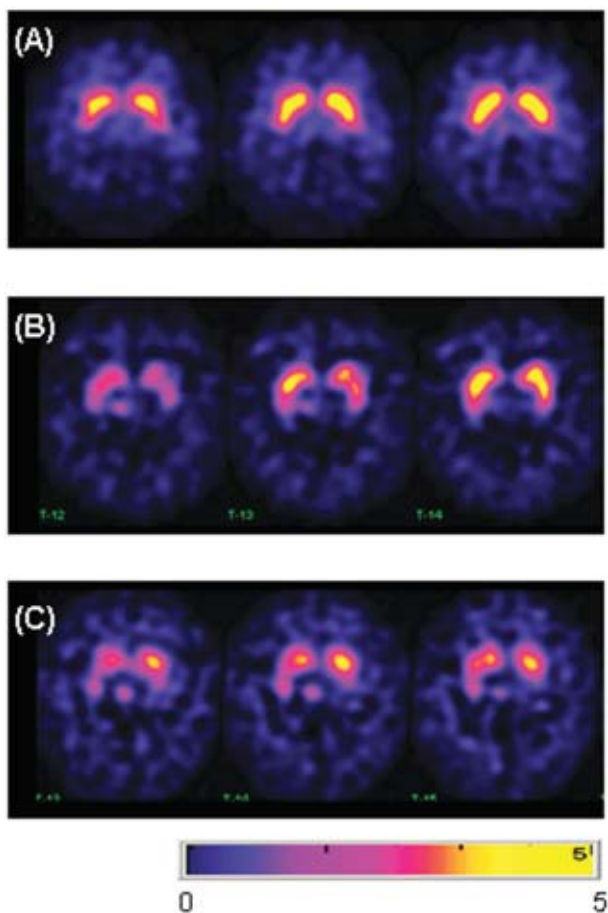
Fig. 2. [^{123}I]-FP-CIT brain SPECT images of dopamine transporter (DAT) taken from the patient (A), a healthy control (B) and a Parkinson's disease patient (PD)(C).

The color bar presents the binding potential (BP) calculated as the ratio of region to occipital uptake. In the patient (A), the overall DAT uptake showed normal range (BP:3.19 (left), 3.20 (right) as compared with those in healthy subjects (mean BP in the striatum: 3.20 ± 0.49, n=12) (B). However, the radiotracer in the putamen showed a mild decrease with scattered small hypodense regions. In a patient with PD (C), a significant reduction of DAT in the putamen was observed.

Discussion

Our case showed predominantly parkinsonian features clearly separated from hepatic encephalopathy episode. Wilson disease was excluded, as were the most frequent causes of secondary parkinsonism, such as vascular, and toxic and drug-induced parkinsonism. Several clinical features allow PD to be reasonably ruled out in our case, such as rapid evolution, absence of resting tremor, symmetry of symptoms, early gait impairment and no response to L-dopa. These clinical features which are important differential points from PD support

manganism[20]. Similarly, atypical parkinsonian syndromes, such as multiple systemic atrophy, progressive supranuclear palsy, or corticobasal degeneration seem unlikely. Our case without occupational history of exposure to Mn showed high level of blood Mn level and T1 hyperintensities in the basal ganglia on MRI. Previous studies[21, 22] demonstrated increased Mn concentrations in pallidum of cirrhotic patients, and suggested that increased Mn concentrations are responsible for T1 hyperintensities in the basal ganglia on MRI. Increased blood Mn level and T1 hyperintensities in the globus pallidus are the principal findings shown in manganism in industrial settings. Moreover, the SPECT finding of overall normal range of DAT uptake in the putamen which is compatible with that of Huang et al.[23] supported manganism. All these findings are compatible with those of manganism, and are remarkably different from those in PD[20, 23–27]. Thus our case could be categorized into secondary manganism due to liver cirrhosis. However, the SPECT finding of scattered small hypodense regions in the putamen despite of an overall normal range of uptake remain to be studied.

To confirm a secondary manganism from hepatic dysfunction, the improvement of abnormal neuroradiological findings after decreased blood Mn by the liver transplantation should be indicated[28]. However, our patient died of liver failure before the liver transplantation. This is a limitation of the present study.

Very recently, Racette et al.[19] reported a manganism due to liver failure who developed a rapidly progressive, symmetric atypical parkinsonism with prolonged L-dopa responsiveness. Her neuroimaging showed relatively symmetric and severely reduced ^{18}F-dopa uptake on PET in the posterior putamen together with T1 hyperintensities in the basal ganglia on MRI. They suggested that the clinical and pathophysiological features of manganism may overlap with that of PD.

There are only two cirrhosis-related parkinsonism cases including ours with fluorodopa PET/DAT SPECT finding to our knowledge[19]. Moreover, their clinical findings and neuroimaging are conflicting. The differences could be explained in two ways. One argument is that the difference would be due to using different imaging modalities (SPECT vs PET). However, SPECT as well as PET shows the integrity of the nigrostriatal dopaminergic system, and is useful in differentiating between manganism and PD[20, 23, 24, 27]. The other argument is a possibility that Racette's patient has PD with incidental Mn exposure. However, pathologic confirmation is not available on the case.

Therefore, further studies are needed to clarify the clinical, neuropathological features and neuroimaging of secondary manganism.

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