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# $^{18}$F-FP-CIT dopamine transporter PET findings in cirrhotic patients with parkinsonism

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ABSTRACT

We report the clinical features and imaging findings of presynaptic dopamine transporter (DAT) positron emission tomography (PET) in four of patients with liver cirrhosis and concurrent parkinsonism. We also reviewed previously reported cases of cirrhosis-related parkinsonism using dopaminergic molecular imaging.

Our results using $^{18}$F-radiolabeled N-(3-fluoropropyl)-2β-carboxymethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) DAT PET in four patients with cirrhosis and parkinsonism showed two different molecular imaging patterns well related to their neurological symptoms. $^{18}$F-FP-CIT PET imaging of two patients showed normal DAT density in the striatum. Their clinical features included symmetric parkinsonism, early gait disturbances and postural instability, and the absence of resting tremor. The other two patients showed reduced striatal DAT uptake asymmetrically with a rostrocaudal gradient similar to idiopathic Parkinson's disease (IPD). They had clinical findings of hemiparkinsonism, resting tremor, without early gait disturbance or postural instability. They also showed sustained response to levodopa treatment.

Based on the structured review of 21 cases with cirrhosis-related parkinsonism in the literature including the present cases, we categorized cirrhotic parkinsonism into three groups. Eleven of the twenty-one cases were categorized into group 1; levodopa-resistant atypical parkinsonism without a dopaminergic deficit in molecular imaging similar to primary manganism. Another 6 cases were categorized into group 2; coincidental IPD with superimposed cirrhosis with sustained good response to levodopa and presynaptic dopaminergic deficit with rostrocaudal gradient typical of IPD. The other undetermined 4 cases were categorized into group 3. They showed symmetric parkinsonism with variable response to levodopa therapy. Their molecular imaging showed a global diffuse dopaminergic deficit in the presynaptic molecular imaging distinct to group 1 (normal uptake) or 2 (asymmetric rostrocaudal deficit). In conclusion, cirrhosis-related parkinsonism is a heterogeneous disorder.



## 1. Introduction

Manganese (Mn) can cause extrapyramidal symptoms including parkinsonism, dystonia, postural instability, or tremor. Mn-induced parkinsonism is classically associated with the occupational exposure in welders, ore miners, smelters, and battery factory workers (Kim et al., 2010a). During past decades, non-occupational Mn exposure, such as liver cirrhosis, prolonged total parenteral nutrition, *SLC30A10* genetic mutation-related hypermanganesemia, and intravenous ephedrone abuse have been of growing interest for their association with the parkinsonism related to chronic Mn accumulation in the brain (Guilarte, 2010).

Previous studies reported that bilateral increases in the signal intensities were observed confined mainly to the globus pallidus on T1-weighted magnetic resonance (MR) imaging, in workers exposed to Mn, while non-exposed workers show normal findings (Kim et al., 1999a; Kim, 2006; Racette, 2014). These characteristic bilateral T1 hyperintensities in the globus pallidus are also observed due to impaired hepatobiliary excretion of Mn caused by portal-systemic shunt in patients with cirrhosis who were not

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occupationally exposed to an external source of Mn (Burkhard et al., 2003; Klos et al., 2006). Approximately 4% of patients with advanced cirrhosis also showed parkinsonism, called cirrhosis-related parkinsonism (Tryc et al., 2013).

Cirrhosis-related parkinsonism is clinically distinct from idiopathic Parkinson's disease (IPD) in early postural instability and gait disturbance, symmetrical presentation at disease onset, less responsive to dopaminergic replacement treatment, and the relative absence of resting tremor (Burkhard et al., 2003; Butterworth, 2013). However, molecular imaging to assess the dopaminergic neurotransmission in cirrhosis-related parkinsonism has been limited until recent years and with no consensus (Racette et al., 2005; Kim et al., 2007, 2010b). Several studies based on dopamine transporter (DAT) imaging with single-photon emission computed tomography (SPECT) found normal nigrostriatal dopaminergic function; however, these were limited by the lower resolution of SPECT compared to that of the contemporary positron emission tomography (PET) technique (Erro et al., 2013; Kim et al., 2010b; Andruska and Racette, 2015). In contrast to prior studies using DAT SPECT, recent reports applying $^{18}$F-labeled fluoro-L-3,4-dihydroxyphenylalanine (FDOPA) PET imaging in two patients with cirrhosis and parkinsonism showed reduced FDOPA uptake in the basal ganglia, suggesting that the spatial resolution of the molecular imaging method could have contributed to the differences among these studies (Racette et al., 2005; Criswell et al., 2012).

$^{18}$F-radiolabeled 2b-carbomethoxy-3b-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT), a high-affinity PET radiotracer for striatal DAT imaging, has superior tracer kinetics than SPECT tracers and has been well established for detecting presynaptic dopaminergic deficit in various parkinsonian syndromes (Kazumata et al., 1998; Park et al., 2014). Therefore, $^{18}$F-FP-CIT PET data may allow the non-invasive assessment of the integrity and change of presynaptic dopaminergic neurotransmission with superior spatial resolutions (Kim et al., 2016).

The objectives of this study were 1) to evaluate cirrhosis-related parkinsonism in our patients using $^{18}$F-FP-CIT PET technique, and 2) to review reported cases of cirrhosis-related parkinsonism using molecular imaging of the dopaminergic neurotransmission.

## 2. Case presentation

### 2.1. Study patients

The clinical features and laboratory findings of patients are summarized in Table 1. All patients who were consecutively assessed at our movement disorder clinic for parkinsonism at the Ulsan university hospital between November 1, 2014, and October 31, 2016, with the inclusion criteria of parkinsonism persistent for ≥3 months and liver cirrhosis assessed by an Ulsan university hospital hepatologist. Parkinsonism was clinically defined by the presence of bradykinesia and at least one of the following symptoms or signs: resting tremor, rigidity, or postural instability. Four patients (3 women) with concurrent liver cirrhosis and parkinsonism were included in the study during this 2-year period, and informed consent to participate was obtained from the patients. Patients' age ranged from 52 to 75 years, and all patients denied any occupational or environmental exposure to an external source of Mn. Herein, we present a brief description of the cases.

Patient 1 (**P1**) was a 57-year-old woman presented with a 4-month history of postural tremor in both arms and gait disturbance. Her medical history was significant for alcoholic liver cirrhosis at the age of 50, complicated by several episodes of hepatic encephalopathy, and evaluated for liver transplantation. Neurologic examinations showed bilateral hand postural tremor, both bradykinesia; stooped posture; hypomimia; and postural instability. There was no weakness or sensory deficit. Laboratory tests indicated abnormal liver function including total bilirubin 2.2 mg/dL (reference range, 0.1–1.2 mg/dL), aspartate aminotransferase (AST) 25 U/L (reference range, 15–40 U/L), alanine aminotransferase (ALT) 12 U/L (reference range, 5–45 U/L), serum albumin 2.6 g/dL (reference range, 3.5–5.0 g/dL), and prothrombin time 13.7 s (reference range, 9.3–13.2 s) with international normalized ratio (INR) 1.19 (reference range, 0.84–1.16). The patient refused to undergo levodopa replacement therapy because liver transplantation was scheduled.

Patient 2 (**P2**) was a 52-year old man who was admitted to our hospital with the symmetric rigid bradykinetic syndrome, postural and/or kinetic tremor in both arms, dysarthria, dysmetria of upper extremities, and progressive gait impairment of 5-month duration. His medical history was significant for chronic hepatitis B for 4 years and irregular medical follow-up. His liver function test on admission disclosed abnormality with total bilirubin 3.4 mg/dL, AST 59 U/L, ALT 36 U/L, serum albumin 2.8 g/dL, and prothrombin time 15.0 s (INR 1.30), compatible with the cirrhosis Child-Pugh class B. Serum copper and ceruloplasmin levels were within the normal range. A liver CT and abdominal sonography findings were consistent with cirrhosis with splenomegaly, portal hypertension, coronary varix gastrorenal and gastrosplenic shunt, and he was newly diagnosed with hepatitis B-related cirrhosis. The patient was not started on levodopa replacement therapy since liver transplantation was scheduled.

Patient 3 (**P3**) was a 69-year-old woman who presented with resting tremor on the right arm and leg, the rigidity of the limbs,

**Table 1**
Clinical features in the four patients with cirrhosis-related parkinsonism.

| Clinical characteristic | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|---|---|---|---|---|
| Age at onset, y/Gender | 57/F | 52/M | 69/F | 75/F |
| Etiology of liver cirrhosis | Alcoholic | Hepatitis B | Cryptogenic | Hepatitis B |
| Duration of parkinsonian symptoms, mo | 4 | 5 | 12 | 5 |
| Clinical symmetry | + | + | – | – |
| Bradykinesia | + | + | + | + |
| Rigidity | + | + | + | + |
| Resting tremor | – | – | + | – |
| Postural and/or intention tremor | + | + | – | + |
| Postural instability | + | + | – | – |
| Gait impairment | + | + | – | – |
| Dysarthria | – | + | – | – |
| Dystonia | – | – | – | – |
| Chorea | – | – | – | – |
| Response to levodopa | not performed | not performed | yes | yes |
| Modified H-Y stage | 2 | 3 | 1.5 | 2 |

–, absent; +, present; H-Y, Hoehn and Yahr.

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