Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0573-17
Intern Med 57: 2719-2722, 2018
http://internmed.jp

【 CASE REPORT 】

# Fatal Familial Insomnia Initially Developing Parkinsonism Mimicking Dementia with Lewy Bodies

Takuya Fukuoka, Yoshihiko Nakazato, Masaomi Yamamoto, Akifumi Miyake, Takashi Mitsufuji and Toshimasa Yamamoto

**Abstract:**
We report a rare case of fatal familial insomnia in a 58-year-old man who initially developed parkinsonism, secondary dementia, and visual hallucinations that were suspected to be due to dementia with Lewy bodies. We evaluated the function of the striatum via dopamine transporter single-photon emission computed tomography (DAT SPECT) using $^{123}$I-ioflupane and found marked presynaptic dopamine dysfunction in the bilateral striatum. This is the first reported case in which the initial symptom of fatal familial insomnia was parkinsonism and in which the dopamine transporter function was evaluated by DAT SPECT.

**Key words:** fatal familial insomnia, parkinsonism, DAT SPECT

**(Intern Med 57: 2719-2722, 2018)**
**(DOI: 10.2169/internalmedicine.0573-17)**

## Introduction

Fatal familial insomnia (FFI) is a rare, neurodegenerative and autosomal dominant prion disease. The initial manifestation in patients with this disease is usually insomnia (1). It is linked to an aspartic acid to asparagine substitution (D178 N) mutation at codon 178 of the prion protein gene (*PRNP*), in conjunction with methionine at the polymorphic position 129 of the mutant allele (2, 3). As the disease progresses, motor disturbances such as myoclonus, ataxia, and spasticity occur, as well as dysarthria and dysphagia (3-6). In addition, parkinsonism can be a symptom of FFI. We herein report a rare case of FFI that initially manifested as parkinsonism mimicking dementia with Lewy bodies (DLB). We evaluated the function of the dopamine nerve terminals in the striatum using dopamine transporter single-photon emission computed tomography (DAT SPECT) using $^{123}$I-ioflupane. The function of the dopamine nerve terminals in patients with FFI has not previously been described.

## Case Report

A 58-year-old man presented to our hospital with a 4-month history of a weak voice, a 3-month history of significant (20 kg) weight loss, short-stepped gait, and repetitive mistakes at work; and a 2-month history of visual hallucinations (worms or worm-like visions and masked face). His familial medical history revealed that his mother may have died from Creutzfeldt-Jakob disease at 60 years of age; however, her detailed medical history was unavailable. The patient initially had no dysautonomia that might have induced hyperhidrosis, hyperthermia, tachycardia, or hypertension, and no insomnia. On admission, his body temperature was 36.4°C, his blood pressure was 150/77 mmHg, and his pulse rate was 72 bpm. A neurologic examination revealed dementia [Mini-Mental State Examination (MMSE) score: 13], visual hallucinations and parkinsonism (tremor, rigidity, bradykinesia, short-stepped gait and postural instability). The other neurological findings ware normal. Serologic tests were negative, and his paraneoplastic and thyroid antibody levels were normal. A routine cerebrospinal fluid analysis revealed normal results and cerebrospinal fluid was negative 14-3-3 protein. Brain T1-weighted magnetic resonance imaging (MRI) disclosed slight diffuse cortical atrophy; diffusion MRI revealed no abnormal findings. Technetium-99m ethyl cysteinate dimer SPECT indicated a decline in the blood perfusion of the cerebral cortex and bilateral thalamus. Polysomnography indicated a reduction in total sleep time, lack of rapid eye movement (REM) sleep, and in-

Department of Neurology, Saitama Medical University, Japan
Received: November 28, 2017; Accepted: January 25, 2018; Advance Publication by J-STAGE: April 27, 2018
Correspondence to Dr. Takuya Fukuoka, tfukuoka@saitama-med.ac.jp

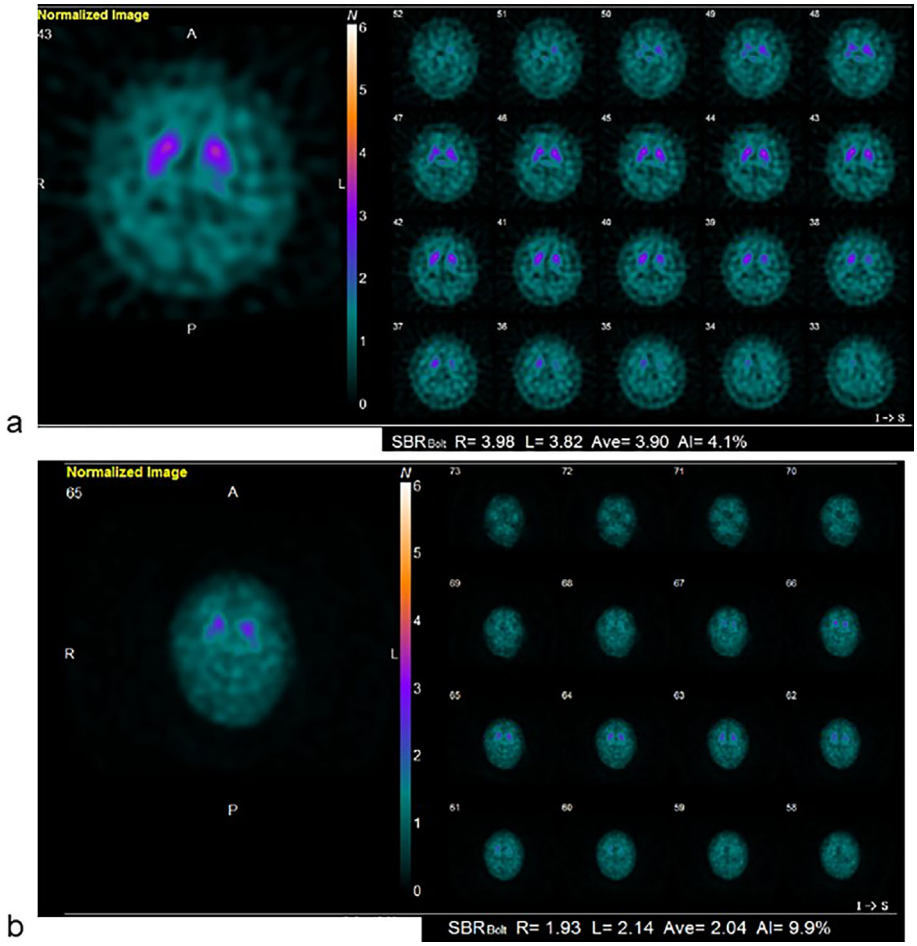


**Figure.** **DAT SPECT findings in a case of fatal familial insomnia with parkinsonism. DAT SPECT imaging at (a) 4 and (b) 5 months after the onset of symptoms. The specific binding ratios (SBRs) were right=3.98, left=3.82 in (a) and right=1.93, left=2.14 in (b). An SBRs of 4.5 is the threshold for dysfunction in our institution. DAT SPECT: dopamine transporter single-photon emission computed tomography**

creased arousal. Electroencephalogram (EEG) showed diffuse slow waves without periodic spike discharges. We performed two further SPECT examinations using $^{123}$I-ioflupane as a marker for dopamine transporter binding at 4 months and 5 months after the onset of symptoms. The specific binding ratios (SBRs) of the right and left sides were 3.98 and 3.82, respectively, at 4 months; and 1.93 and 2.14 (right and left, respectively) at 5 months (Figure). The threshold for normal function in our institution was 4.5; thus, the presynaptic striatal dopaminergic nerve terminals showed a decreased function, which declined rapidly over the month between tests.

We initially suspected that the patient might have DLB based on the parkinsonism and visual hallucinations, despite the fact that his clinical symptoms progressed more rapidly in comparison to typical DLB. We prescribed levodopa (peak dose: 1,200 mg/day) during the 2 months for which he was inpatient; however this was ineffective and his clinical symptoms progressed much more rapidly than the symptoms of a patient with DLB would have. His dementia progressed to the extent that he could not complete the MMSE. Sympathetic autonomic symptoms (hypertension, sweating, remittent fever) and insomnia manifested and progressed during this time. At seven months, the patient demonstrated laryngeal stridor, swallowing dysfunction, and aspiration pneumonia. He required mechanical ventilation, followed by tracheostomy and died due to pneumonia 9 months later. Based on the clinical course, we sequenced DNA extracted from the peripheral blood leukocytes, and identified a D178 N mutation with methionine/methionine homozygosity at the polymorphic codon 129 of *PRNP*. Based on this result we formally diagnosed the patient with FFI.

## Discussion

Our patient was confirmed as having probable FFI, despite initially presenting with parkinsonism, secondary dementia and visual hallucinations that were suspected to have been caused by DLB and was finally diagnosed with FFI based on gene sequencing of DNA. Although three previous reports (5-7) have described FFI patients with parkinsonism (Table), there are no previous reports of cases in which parkinsonism was the initial symptom of FFI.

DAT SPECT imaging assesses the functional status of the

**Table. Past Reports of Fatal Familial Insomnia Presenting with Parkinsonism.**

| Reference No. | Age/sex | Initial symptoms | Parkinsonian symptoms | polymorphic codon 129 of prion protein gene |
|---|---|---|---|---|
| 6 | 67/F | diplopia, insomnia, excessive daytime sleepiness, progressive gait ataxia, and slurred speech | tremor, bradykinesia, rigidity, and postural instability | methionine/valine |
| 5 | 52/M | insomnia | Latero/retropulsion | methionine/methionine |
| | 62/M | insomnia | Latero/retropulsion | methionine/methionine |
| 7 | 55/M | Not described | Parkinsonism | methionine/methionine |
| Our case | 58/M | Bradykinesia and short-stepped gait | bradykinesia, short-stepped gait, and postural instability | methionine/methionine |

nigrostriatal dopaminergic system, and can provide a marker of presynaptic neuronal degeneration. A reduced striatal uptake (i.e., lower DAT SBRs) is associated with extrapyramidal signs, such as bradykinesia and rigidity (8); in this patient the DAT SBRs were initially below the threshold for dysfunction at our instiution, and rapidly worsened. DAT SPECT revealed the dysfunction of the presynaptic dopamine neurons in the striatum. Levodopa had no effect on the patient's parkinsonism. These findings demonstrate damage of both presynaptic and postsynaptic dopaminergic systems. Klöppel et al. reported two cases of FFI without parkinsonism that were examined by 2-β-carbomethoxy-3-β-(4-iodophenyl)-tropane (β-CIT) SPECT. They reported that β-CIT SPECT showed a region-specific uptake with the highest activity in the striatum, which corresponded to striatal dopamine transporters, suggesting a normal presynaptic dopamine system (9). However, DAT SPECT imaging of the presynaptic dopamine neurons with the ligand $^{123}$I-2-β-carbometoxy-3-β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane ($^{123}$I-FP-CIT), which binds to the DAT reuptake site and visualizes the presynaptic function related to the parkinsonism. DAT SPECT could directly evaluate the presynaptic neuronal degeneration and the reduced striatal uptake, and thus provided high sensitivity in the detection of parkinsonism in FFI. Atrophy of the anterior ventral and mediodorsal nuclei of the thalamus, which can be observed by a histopathological examination, remains the most prominent change in FFI; however, various degrees of atrophy and reactive astrogliosis have been found in other thalamic nuclei, the cerebral and cerebellar cortexes, and the olives (3). Moreover, apoptotic neurons were also found in the neocortex and striatum of FFI patients who are heterozygous (methionine/valine) for the polymorphism at codon 129 (M129V) of *PRNP*, who demonstrate a longer disease duration and more widespread cerebral changes. In contrast, in patients who are homozygous for the polymorphism at codon 129 (M129M) of *PRNP*, the involvement of the cerebral cortex and striatum was reported to generally be inconspicuous and restricted to inconstant rare spongiform change (10). We could find marked presynaptic dopamine dysfunction in the bilateral striatum using DAT SPECT, even if the striatum change was generally pathologically inconspicuous in this case of homozygous FFI. Furthermore, this FFI patient presented with parkinsonism in both M129M and M129V (Table).

Generally, the initial symptom of FFI is insomnia. In our case, the initial symptom was parkinsonism, while another report on FFI described a unique case in which the initial symptom was dementia (11). Thus, the initial symptoms of FFI are considered to be heterogeneous. Our case emphasizes the possibility that isolated parkinsonism may occur as an initial symptom in FFI, instead of insomnia; however, this parkinsonism was refractory to levodopa therapy and progressed rapidly, which differentiated it from DLB or other diseases associated with parkinsonian symptoms.

**The authors state that they have no Conflict of Interest (COI).**

**Acknowledgement**

We would like to thank Prof. Tetsuyuki Kitamoto (Department of Neurological Science, Tohoku University) for the *PRNP* analysis and Prof. Katsuya Satoh (Department of Locomotive Rehabilitation Sciences, Nagasaki University Graduate School of Medicine) for the 14-3-3 protein detection.

## *References*

1. Shi XH, Han J, Zhang J, et al. Clinical, histopathological and genetic studies in a family with fatal familial insomnia. Infect Genet Evol **10**: 292-297, 2010.
2. Goldfarb LG, Petersen RB, Tabaton M, et al. Fatal familial insomnia and familial Creutzfeldt-Jakob disease: disease phenotype determined by a DNA polymorphism. Science **258**: 806-808, 1992.
3. Medori R, Tritschler HJ, LeBlanc A, et al. Fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene. N Engl J Med **326**: 444-449, 1992.
4. Gallassi R, Morreale A, Montagna P, Gambetti P, Lugaresi E. "Fatal familial insomnia": neuropsychological study of a disease with thalamic degeneration. Cortex **28**: 175-187, 1992.
5. Cortelli P, Fabbri M, Calandra-Buonaura G, et al. Gait disorders in fatal familial insomnia. Mov Disord **29**: 420-424, 2014.
6. Pedroso JL, Pinto WB, Souza PV, et al. Complex movement disorders in fatal familial insomnia: a clinical and genetic discussion. Neurology **81**: 1098-1099, 2013.
7. Wu L, Lu H, Wang X, et al. Clinical features and sleep analysis of Chinese patients with fatal familial insomnia. Sci Rep **7**: 3625, 2017.
8. Marshall V, Grosset D. Role of dopamine transporter imaging in routine clinical practice. Mov Disord **18**: 1415-1423, 2003.
9. Klöppel S, Pirker W, Brucke T, Kovacs GG, Almer G. Beta-CIT SPECT demonstrates reduced availability of serotonin transporters in patients with Fatal Familial Insomnia. J Neural Transm (Vienna) **109**: 1105-1110, 2002.
10. Dorandeu A, Wingertsmann L, Chretien F, et al. Neuronal apopto-

sis in fatal familial insomnia. Brain Pathol **8**: 531-537, 1998.

**11.** Saitoh Y, Ogawa M, Naito Y, et al. Discordant clinicopathologic phenotypes in a Japanese kindred of fatal familial insomnia. Neurology **74**: 86-89, 2010.