CASE REPORT

Fatal Familial Insomnia Initially Developing Parkinsonism Mimicking Dementia with Lewy Bodies

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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

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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 (D178N) 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 were 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 ins...
Increased 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 D178N 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

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**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.
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 institution, 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 damage of both presynaptic and postsynaptic dopaminergic systems in the patient’s parkinsonism. These findings demonstrate damage of both presynaptic and postsynaptic dopaminergic systems.

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

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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/methionine/methionine/methionine/methionine |
| 6             | 62/M    | insomnia         | Latero/retropulsion    | methionine/methionine/methionine/methionine/methionine/methionine |
| 7             | 55/M    | Not described    | Parkinsonism           | methionine/methionine/methionine/methionine/methionine/methionine |
| Our case      | 58/M    | Bradykinesia and short-stepped gait | bradykinesia, short-stepped gait, and postural instability | methionine/methionine/methionine/methionine/methionine/methionine |

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.
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