

[CASE REPORT]

A Japanese Encephalitis Patient Presenting with Parkinsonism with Corresponding Laterality of Magnetic Resonance and Dopamine Transporter Imaging Findings

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Abstract:

Japanese encephalitis (JE) survivors often present with nigrostriatal aftereffects with parkinsonian features. A 67-year-old woman with JE showed right-dominant clinical parkinsonism and left-dominant substantia nigra lesions after magnetic resonance imaging (MRI). Dopamine transporter (DAT) imaging using ¹²³I-labeled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropine (¹²³I-FP-CIT) revealed a corresponding left-dominant decrease. The present case is the first to reveal a clear match of laterality between clinical parkinsonism, MRI-based substantia nigra lesions, and impaired DAT in presynaptic dopaminergic neurons in JE.

Key words: Japanese encephalitis, parkinsonism, DAT, ¹²³I-FP-CIT

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Introduction

Japanese encephalitis (JE) is the most serious infectious disease of the central nervous system. Approximately 15% of JE patients die during the acute phase of the illness, and most survivors present with neurological aftereffects, including striatal dysfunctions and parkinsonian features (1). Presynaptic striatal dysfunctions recently became detectable by dopamine transporter (DAT) imaging, which is usually applied to neurodegenerative disorders such as Parkinson's disease and progressive supranuclear palsy (PSP). However, there are only limited reports of DAT imaging for JE patients (2, 3). In this paper, we report a JE patient that presented with parkinsonism, with decreased DAT imaging using a new radiotracer. The patient showed clear corresponding laterality of clinical parkinsonism, MRI-based substantia nigra lesions, and DAT.

Case Report

A 67-year-old Japanese woman was admitted to our hospital after 4 days of a fever at 38.6°C. Upon admission (Day 5), she showed a high fever (40.1°C), confusion, and delirium. Neurological examinations revealed impaired consciousness (Japan coma scale I-3 and Glasgow coma scale E4V4M5), saccadic eye tracking, hyperreflexia in all extremities, neck stiffness, and positive Kernig's sign. She also showed parkinsonian features, such as bradykinesia, a masked face, microphonia, bilateral resting tremor in the hands (right>left), and rigidity in all extremities (right>left). A laboratory blood test showed mild inflammatory reactions with an erythrocyte sedimentation rate (ESR) of 40/71 mm (1 and 2 hours), a white blood-cell (WBC) count of 13,800 μL, and 2.48 mg/dL of C-reactive protein (CRP). A cerebrospinal fluid (CSF) analysis showed pleocytosis (260/μL,

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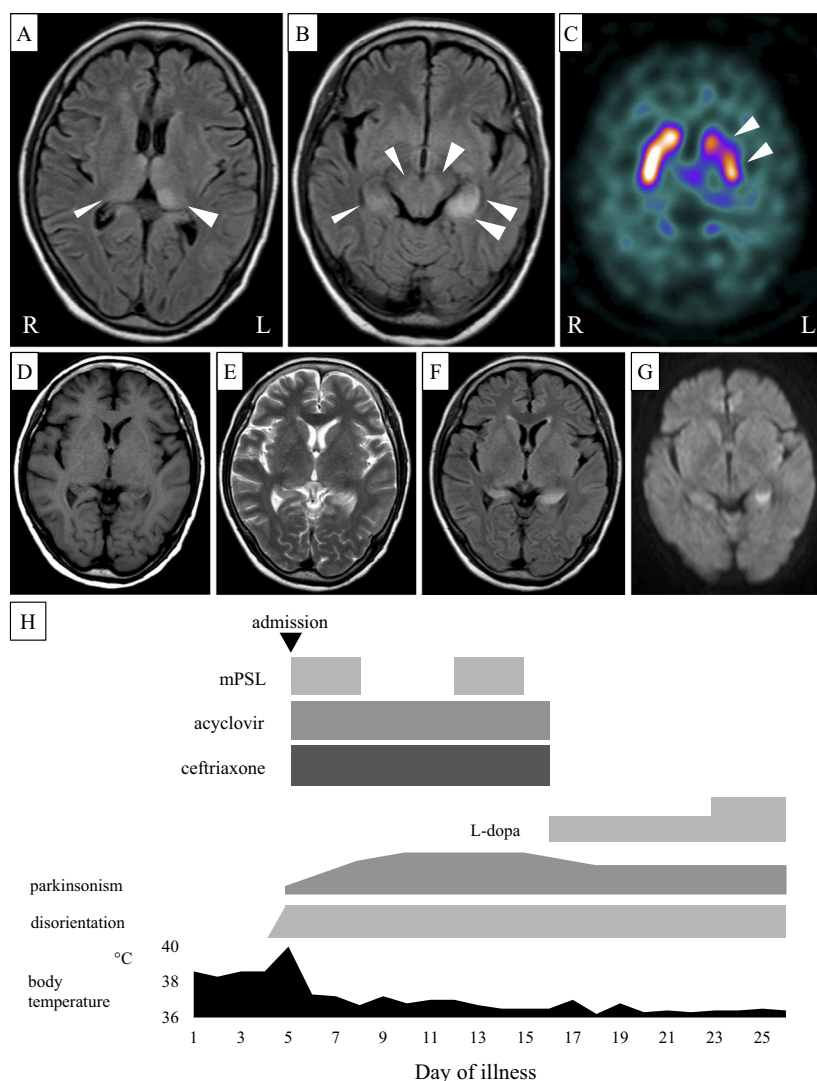


Figure. (A, B) Brain MRI FLAIR images, showing high-intensity bilateral lesions in the thalamus on day 9 (A, arrowheads), substantia nigra, and medial temporal lobes (right<left) (B, arrowheads). (C) DAT imaging with ^{123}I -FP-CIT, revealing a decrease in the uptake, predominantly in the left striatum (arrowheads). (D-G) Note the lack of lesions in the striatum on brain MRI with T1- (D) and T2-weighted (E), FLAIR (F) or DWI (G) images. (H) The clinical course of the present case. After four days of a high fever, the patient developed parkinsonism and disorientation. Levodopa therapy improved her parkinsonism.

Table 1. Serological Test for Japanese Encephalitis.

	Acute phase	Convalescent phase	
JEV-IgM (ELISA)	7.22 (day5)	9.76 (day20)	(cut off:>2.0)
Hemagglutination inhibition test	1:20 (day12)	1:640 (day20)	
Neutralization test	1:80 (day5)	1:2,560 (day20)	

JEV: Japanese encephalitis virus

mononuclear, 82% and polynuclear, 18%), elevated protein (137 mg/dL), and mildly reduced glucose (67 mg/dL; serum glucose 183 mg/dL). Brain magnetic resonance imaging (MRI) on day 9 revealed bilateral high-intensity lesions (left > right) in the medial temporal lobes, thalamus, and sub-

stantia nigra on a fluid-attenuated inversion recovery (FLAIR) image (Figure A and B, arrowheads).

Since herpes simplex or bacterial meningoencephalitis were initially suspected, we started acyclovir and antibiotics (ceftriaxone) combined with methylprednisolone pulse therapy. After these treatments, the high fever improved (Figure H), but there was no change in the consciousness disturbance, and the parkinsonism worsened, especially the rigidity of the right upper and lower extremities (Figure H). An enzyme-linked immunosorbent assay (ELISA) detected Japanese encephalitis virus (JEV)-specific IgM in both the serum (7.22 index, cut off >2.0) and CSF (8.65 index) on day 5 of the illness. She was diagnosed with JE, which was confirmed by a hemagglutination inhibition test and a neutralization test during the convalescent phase (Table 1).

Dopamine transporter (DAT) imaging using ^{123}I -labeled

Table 2. Clinical and Radiological Summary of Japanese Encephalitis Patients.

	Ref. 2			Ref. 3	The present case (Japan)
	Case 1	Case 2	Case 3		
Age (Y)	20	21	28	65	67
Gender	Male	Male	Male	Female	Female
Country	Taiwan	Taiwan	Taiwan	Taiwan	Japan
Tremor	+	+	+	+	+
Hypokinesia	+	+	+	+	+
Hypophonia	+	+	+	n.m.	+
Masked face	+	+	+	n.m.	+
Rigidity	+	+	+/-	n.m.	+
Dyskinesia	-	-	+	n.m.	-
Dystonia	+	-	-	n.m.	-
Lateral severity	rt=lt	rt>lt	rt=lt	n.m.	rt>lt
Substantia nigra lesions on MRI	rt<lt	rt>lt	rt>lt	n.m.	rt<lt
DAT-SPECT radiotracer	^{99m} Tc-TRODAT-1	^{99m} Tc-TRODAT-1	^{99m} Tc-TRODAT-1	^{99m} Tc-TRODAT-1	¹²³ I-FP-CIT
DAT-SPECT finding	bil. decreased (rt<lt)	bil. decreased (rt>lt)	bil. decreased (rt>lt)	bil. decreased (rt<lt)	lt. decreased
¹²³ I-IBZM SPECT finding	bil. decreased (rt>lt)	bil. decreased (rt<lt)	bil. increased (rt=lt)	n.a.	n.a.

n.m.: not mentioned, n.a.: not assessed

2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropine (¹²³I-FP-CIT) on day 24 of the illness revealed a decreased uptake in the left striatum (Figure C, arrowheads), whereas brain MRI revealed no corresponding striatal lesion on T1- or T2-weighted imaging, FLAIR, or diffusion-weighted imaging (DWI) (Figure D-G). The patient's parkinsonism was improved by levodopa (150 mg/day) therapy, so she was transferred to another hospital for rehabilitation on the 22nd day of hospitalization (Figure H).

Discussion

Parkinsonism is one of the most common symptoms of JE patients, being present in as many as 45% of cases (1). Brain computed tomography (CT) and MRI studies often reveal lesions in the thalamus, basal ganglia, and midbrain (4). Srivastava et al. showed an affinity of JEV to the thalamus and midbrain after discovering a number of RNA copies of JEV in a rat model of JE (5).

Liao et al. showed the involvement of the nigrostriatal pathway in three JE patients presenting with parkinsonism in Taiwan by single-photon emission tomography (SPECT) using the radiotracer ^{99m}Tc-TRODAT-1 for DAT imaging, and ¹²³I-iodobenzamide (¹²³I-IBZM) for D2 dopamine receptor imaging (Table 2) (2). All three patients showed bilateral substantia nigra lesions on brain MRI, albeit at different severities, but these did not reflect the corresponding clinical laterality. The decrease in DAT laterality did not simultaneously present as clinical laterality in cases 1 and 3 and was even reversed in case 2 (Table 2). In contrast, ¹²³I-IBZM SPECT showed a decreased uptake in the striatum of cases 1 and 2, but an increased uptake in case 3. The laterality of the decrease in the D2 dopamine receptor corresponded to clinical laterality only in case 2, not in cases 1 or 3. How-

ever, in case 3, the increased uptake of ¹²³I-IBZM SPECT compensated for the laterality of its decreased DAT laterality. Another report from Taiwan also showed decreased DAT laterality in a JE patient using the same radiotracer, ^{99m}Tc-TRODAT-1, but the laterality of parkinsonism was not described (3).

In the present case, DAT imaging with a different radiotracer, ¹²³I-FP-CIT, revealed a left-dominant decrease (Figure C, arrowheads) corresponding to right-dominant clinical parkinsonism and left-dominant substantia nigra lesions on MRI (Figure B, arrowheads). Both ¹²³I-FP-CIT and ^{99m}Tc-TRODAT-1 are cocaine analogs that bind to DAT, but ¹²³I-FP-CIT may be more accurate for the diagnosis of degenerative extrapyramidal disorders than ^{99m}Tc-TRODAT-1 (6). The present report shows that DAT imaging with ¹²³I-FP-CIT can clearly reveal the laterality of impaired presynaptic dopaminergic neurons corresponding to the laterality of clinical parkinsonism and MRI-based substantia nigra lesions in JE.

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

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