Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.5743-20
Intern Med 60: 941-944, 2021
http://internmed.jp

【 CASE REPORT 】

Temporal Changes in Brain Perfusion in Neuronal Intranuclear Inclusion Disease

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Abstract:
We herein report a patient with neuronal intranuclear inclusion disease (NIID) who presented with encephalitis-like episodes. A neurological examination revealed a disturbance of consciousness without any evidence of encephalitis or epilepsy on laboratory tests. Brain perfusion single-photon emission computed tomography revealed an elevated cerebral blood flow during the encephalitis-like episode and reduced cerebral blood flow in the chronic phase with clinical recovery. This report suggests that the cerebral blood flow of patients with NIID can change over the clinical course. Encephalitis-like episodes of NIID should thus be considered in the differential diagnosis of acute disturbance of consciousness.

Key words: NIID, SPECT, cerebral blood flow, skin biopsy, leukoencephalopathy, disturbance of consciousness

(Intern Med 60: 941-944, 2021)
(DOI: 10.2169/internalmedicine.5743-20)

Introduction

Neuronal intranuclear inclusion disease (NIID) is a gradually progressive neurodegenerative disease that clinically manifests as progressive cognitive impairment, pyramidal signs, peripheral nervous disorders, and disturbance of consciousness (1). Other characteristics of NIID include leukoencephalopathy on T2 and fluid-attenuated inversion recovery images, as well as high-intensity lesions along the corticomedullary junction on diffusion-weighted imaging (DWI) (2). In addition, pathological findings reveal myelin pallor and multiple focal spongiotic changes in the white matter adjacent to the cerebral cortex, corresponding to high-intensity lesions on DWI and eosinophilic intranuclear inclusions in neurons and astrocytes (1). Patients with NIID sometimes exhibit encephalitis-like episodes and focal brain edema on magnetic resonance imaging (MRI) (2); however, the pathophysiology of these episodes remains unclear.

We herein report a patient with NIID who presented with an encephalitis-like episode. During the clinical course, brain perfusion single-photon emission computed tomography (SPECT) detected temporal changes in the cerebral blood flow.

Case Report

A 75-year-old woman presented with a disturbance of consciousness and a fever. She had some history of episodic disturbance of consciousness, and her cognitive impairment had gradually progressed since the first episode. Her family history was unremarkable.

A neurological examination revealed a disturbance of consciousness and loss of tendon reflexes. However, routine laboratory tests, including those for the presence of infectious, autoimmune, and metabolic diseases, presented standard results. An analysis of the cerebrospinal fluid (CSF) revealed a marginal increase in the total protein (42.4 mg/dL; reference, <40 mg/dL) without an increase in the cell count or decrease in blood glucose levels. The IgG index was standard, and electroencephalography (EEG) displayed neither electrical activity nor epileptic discharge in the left hemisphere. Brain MRI revealed swelling (Figure A) and linear high-intensity lesions in the corticomedullary junction of the left hemisphere on DWI (Figure B).

After admission, the disturbance of consciousness continued for one week. A histological examination of a skin biopsy specimen showed ubiquitin-positive eosinophilic in-

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Received: July 2, 2020; Accepted: September 6, 2020; Advance Publication by J-STAGE: October 21, 2020
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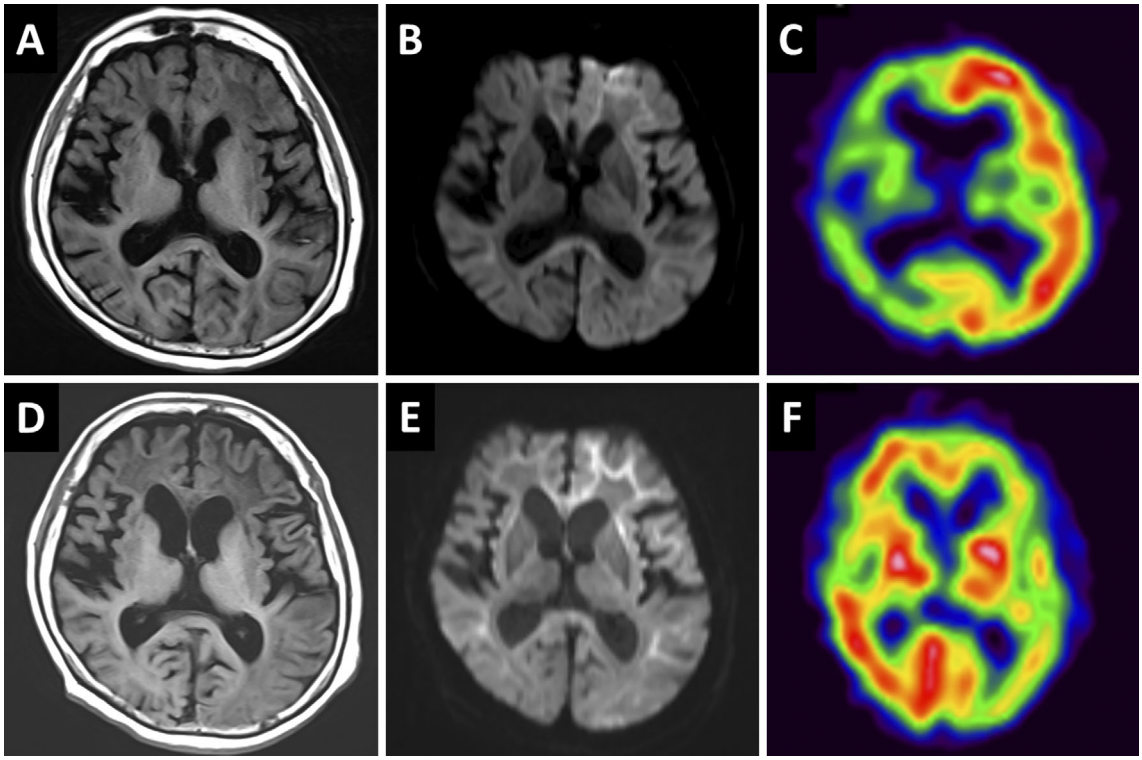

Figure. **Brain axial T1-weighted imaging, diffusion-weighted imaging (DWI), and single-photon emission computer tomography (SPECT). (A) Axial T1-weighted imaging shows brain swelling in the left hemisphere. (B) DWI shows lesions in the corticomedullary junction of the left hemisphere. (C) SPECT shows hyperperfusion in the left hemisphere during the encephalitis-like episode. One month later, T1-weighted imaging shows progressive brain atrophy in the left hemisphere (D), the lesions on DWI have extended to the contralateral hemisphere (E), and hypoperfusion is notable in the chronic phase (F).**

tranuclear inclusions in dermal cells. Although genetic testing was not performed, she was diagnosed with NIID based on the characteristic MRI findings and pathological findings of skin biopsy. Technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD) SPECT at seven days after the onset revealed an increased cerebral blood flow in the left hemisphere (Figure C), following which the disturbance of consciousness and fever gradually improved.

Despite suspicions of nonconvulsive seizure, EEG revealed low-voltage activities without epileptic discharge in the left hemisphere. Follow-up MRI at 30 days after the onset revealed progressive brain atrophy in the left hemisphere (Figure D), and the high-intensity lesions on DWI extended to the contralateral hemisphere (Figure E). SPECT at 60 days after the onset showed a decreased cerebral blood flow in the left hemisphere (Figure F).

Discussion

We encountered a case of NIID with temporal changes in brain perfusion SPECT findings. Although genetic testing was not performed, stroke, autoimmune diseases, demyelinating diseases, infectious encephalitis, seizure, intoxication, and metabolic encephalopathies were ruled out based on laboratory and radiological findings. This case displayed an increased cerebral blood flow on SPECT in the left hemisphere, along with high-intensity lesions on DWI during the encephalitis-like episode. In addition, follow-up SPECT after two months revealed a reduced cerebral blood flow in the left hemisphere, although high-intensity lesions on DWI had spread to the entire brain. Notably, the range of the temporal changes in the cerebral blood flow on SPECT was wider than that of the high-intensity lesions on DWI. This is the first case in which brain perfusion SPECT was examined repeatedly during the clinical course.

The most significant finding of our case is the temporal changes in the cerebral blood flow, which increased during the encephalitis-like episode but decreased in the chronic phase. Some studies have reported the MRI and brain perfusion SPECT findings during encephalitis-like episodes in patients with NIID (3-5). One study showed a decreased cerebral blood flow on arterial spin labeling and arterial constriction on magnetic resonance angiography (MRA) at the onset of encephalitis-like episodes (3). Another study showed the arterial constriction on MRA at the onset of encephalitis-like episodes, and arterial constriction was improved the following day (4). Previous SPECT studies have shown an increased cerebral blood flow at three (3) or seven days (5) after the onset of encephalitis-like episodes. Our SPECT findings at seven days after the onset of

encephalitis-like episodes is consistent with those of previous studies. Furthermore, almost all previous reports of brain perfusion SPECT in patients with NIID reported progressive cognitive impairment and a reduced cerebral blood flow in the chronic phase (2), which is consistent with our case exhibiting a decreased cerebral blood flow two months after the onset.

Our SPECT study used agent ^{99m}Tc-ECD, which is a safe, effective, and radiochemical stable marker of the regional cerebral blood flow and precisely detects subtle focal changes in the cortical uptake (6, 7). The ^{99m}Tc-ECD distribution was able to depict not only brain perfusion but also the enzymatic process reduction because of neuronal dysfunction due to the trapping of ^{99m}Tc-ECD in abnormal neurons for a prolonged period (8, 9). Thus, reduced ^{99m}Tc-ECD in the chronic phase reflects brain atrophy with neuronal loss in our patient. However, the pathophysiology underlying the increased ^{99m}Tc-ECD uptake in the encephalitis-like phase remains unclear.

The increased ^{99m}Tc-ECD uptake in our patient might not reflect inflammation based on the normal cell counts in the CSF. Reportedly, the pathological findings in patients with NIID show myelin pallor and multiple focal spongiotic changes without inflammation (1). Furthermore, patients with convulsion exhibit a compensatory increased cerebral blood flow because of the elevated glucose and O_2 needed during prolonged overactivation of epileptic neurons (10, 11). However, our patient exhibited no epileptic discharge on EEG.

Previous MRA findings of patients with NIID showed arterial constriction on MRA at the onset of encephalitis-like episodes (3, 4). Furthermore, one patient showed improvement in arterial constriction the following day (4). Therefore, the increased ^{99m}Tc-ECD uptake in our patient may be attributed to luxury hyperperfusion, which is an increased cerebral blood flow in the ischemic lesions within about one month after the onset of stroke (12, 13). Ischemia damages neurons, resulting in the release of some vasodilators, including potassium, bradykinin, adenosine, arachidonate, nitric acid, and oxygen radicals. In addition, patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) present with a decreased cerebral blood flow in the hyperacute stage (within three hours after the onset) of stroke-like episodes, increased cerebral blood flow in the acute stage (within one month), and reduced cerebral blood flow in the chronic stage (several months later) (14). A decreased cerebral blood flow in the hyperacute stage reflects the segmental impairment of vasodilation due to mitochondria angiopathy, whereas the increased cerebral blood flow in the acute stage reflects the compensatory response against transient ischemia or neuronal hyperexcitability (14). Therefore, we suggest that the increased ^{99m}Tc-ECD uptake in our patient might reflect luxury hyperperfusion or the compensatory response against transient ischemia, while the decreased ^{99m}Tc-ECD uptake might reflect the long-term neuron dysfunction. Although a previous study reported the stenosis of the middle cerebral artery on MRA (3), we did not assess the brain arteries using MRA in our patient.

Conclusion

We herein report a patient with NIID who presented with an encephalitis-like episode. Further studies, including temporal assessments with multiple modalities, are needed in order to clarify the pathophysiology of NIID. Overall, this case showed temporal changes in the cerebral blood flow on SPECT.

Author's disclosure of potential Conflicts of Interest (COI).
Noriyuki Kimura: Honoraria, Takeda Pharmaceutical and Janssen Pharmaceutical.

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