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Case Report

Imaging findings and pathological correlations of subacute encephalopathy with neuronal intranuclear inclusion disease–Case report ☆,☆☆

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ABSTRACT

Neuronal intranuclear inclusion disease (NIID) is a slowly progressive neurodegenerative disease and may sometimes present with symptoms of subacute encephalopathy, including fever, headache, vomiting, and loss of consciousness. We present a case of adult-onset NIID with subacute encephalopathy, which is confirmed by skin and brain biopsied. The magnetic resonance imaging findings show cortical swelling and hyperintensities in the right temporooccipital lobes on T2-weighted images and magnetic resonance angiography demonstrates vasodilatations of the right middle cerebral artery and posterior cerebral artery. Abnormal enhancement is mainly observed in the gyral crowns (crown enhancement). Pathological examinations reveal new infarcts in the deep layers of the cortices. NIID should be considered in the presence of subacute encephalopathy with cortical swelling, contrast enhancement in the temporooccipital lobes, and vasodilation in adult patients. The encephalopathy targeted on the cortices, and the pathological background included infarctions.

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Introduction

Neuronal intranuclear inclusion disease (NIID) is a slowly progressive neurodegenerative disease that is pathologically characterized by eosinophilic intranuclear inclusions in multiple organs. Hyperintense lesions in the corticomedullary junctions (CMJs) on diffusion-weighted imaging (DWI) are also characteristic of NIID and it is diagnosed via skin biopsy [1,2].

Sporadic and familial cases of NIID have been reported and are classified into 3 subgroups according to age of onset and disease duration: infantile, juvenile, and adult forms. Cognitive dysfunction is observed in the adult-onset group [3]. Sone et al. reported 121 cases of adult-onset NIID (98 sporadic cases and 23 family cases) diagnosed by skin biopsy and autopsy [2]. The patients were classified into 2 groups according to the initial symptoms: muscle weakness and dementia. The majority of patients with sporadic NIID had dementia as the main complaint. Apart from dementia, 58.5% of the patients had myosis, about 47.8% had ataxia, 38% had bladder dysfunction, and 36.5% had prolonged disturbance of consciousness. The mean age of onset was 64.1 years. There have been no comprehensive reports on the prevalence of NIIDs. However, since Sone et al. reported the usefulness of skin biopsy in 2011, prenatal diagnosis of NIID has become possible, and the number of reports is increasing [4].

The characteristic hyperintensities in the CMJs on DWI is a major clue to the diagnosis [5]. A skin biopsy is performed and the diagnosis is based on the presence of nuclear inclusion bodies stained with anti-ubiquitin or anti-p62 antibodies [2,4,5]. Furthermore, in 2019, a study reported that the cause of NIID is CGG repeat elongation of the human-specific gene NOTCH2NLC [6]. At present, there are no appropriate methods to target the pathophysiological mechanism of NIID. Supportive and symptomatic therapy is often used.

Patients with sporadic adult-onset NIID may present subacute encephalopathy, including fever, headache, vomiting, and loss of consciousness [2]. Herein, we report a case of subacute encephalopathy of NIID, with the aim of presenting MRI findings from the patient and demonstrating the correlations between the MR images and pathological findings.

Case report

A 61-year-old woman was admitted to the hospital because her family noticed that she had dysarthria and transient left upper limb paralysis. The patient had parkinsonism for approximately 10 years. Six days before admission, the patient had persistent headaches. After admission, a urinary tract infection was suspected due to a mildly elevated inflammatory response and cloudiness of urine. Treatment with antibiotics was initiated, and the inflammatory response quickly resolved.

Consciousness disturbances remained for 2 weeks, and left facial spasms were noted. Based on the clinical course and imaging findings, encephalitis was suspected, and a brain biopsy was performed on day 22 to confirm the diagnosis. Steroid pulse therapy was then administered for 3 days, followed by maintenance steroid therapy. The patient's consciousness gradually improved, and on day 77, consciousness disturbance disappeared, and she was discharged from the hospital with no further deterioration of symptoms.

DWI performed on admission showed characteristic hyperintense lesions in the CMJs of the bilateral frontoparietal lobes (Fig. 1A) without diffusion restriction. T2-weighted imaging (T2WI) demonstrated cortical swelling and hyperintensities in the right temporooccipital lobes (TOLs) on day 14 (Fig. 1B). DWI showed milder hyperintense cortical lesions in the TOLs (Fig. 1C) without diffusion restriction. Magnetic resonance angiography demonstrated vasodilatations of the right middle cerebral artery and posterior cerebral artery (not shown). T1-weighted imaging after the administration of contrast medium (Fig. 1D) showed cortical enhancement in the right TOLs. Abnormal enhancement was mainly observed in the gyral crowns (ie, crown enhancement) but was absent or only slightly observed in the bottoms of sulci. Abnormal enhancement was also observed in the dura matter adjacent to the cortices. SPECT demonstrated hyperperfusion in the right TOLs (Fig. 1E).

Cortical swelling and hyperintensities disappeared on day 45, and vasodilatations of the right middle cerebral artery and posterior cerebral artery and hyperperfusion in the right TOLs also disappeared. However, T2WIs of the patient demonstrated new hyperintense lesions in the subcortical white matter in the TOLs (Fig. 1F). Additionally, DWI showed milder hyperintense lesions in the CMJs of the same regions (Fig. 1G) without diffusion restriction.

Ten months later, hyperintense lesions in the subcortical white matter on T2WI and milder hyperintensities in the CMJs on DWI both disappeared, and atrophy occurred in the same areas. There were also no abnormal signals in the middle cerebellar peduncles during the disease course.

The patient underwent open brain biopsy of the right temporal lobe on day 22. A 1 cm^2 cortical incision was made in the inferior border of the superior temporal gyrus, and the brain tissue was biopsied to a depth of approximately 1 cm. The cortex was slightly enlarged, and the white matter was soft and edematous. Histologically, a small, recent infarct was detected in the cerebral cortex, continuous with which a lesion was detected in the deep cerebral cortex causing edema, neuronal loss, ischemic changes, proliferation of the vessels with hypertrophic walls, and petechiae (Figs. 2A-C). Immunohistochemical analysis showed marked macrophage/microglia infiltration in the lesion with surrounding astrocytosis. Moreover, ubiquitin- and p62-positive eosinophilic intraneuronal hyaline inclusions were found in the cells of the cortex and white matter, many of which were astrocytes, and some were considered oligodendrocytes. The cells of the arteriolar walls in the cerebral cortex occasionally had small intranuclear inclusions. Furthermore, some arterioles with and without nuclear inclusions had thickened walls and luminal stenosis. Small intranuclear inclusions were also occasionally noted in the vascular walls of the arachnoid and dura mater.

The skin and muscle biopsies showed eosinophilic intranuclear inclusions in the sweat glands, arrector pili muscle, dermal fibroblasts, vascular walls, and adipocytes. No ragged red muscle fibers or mitochondrial gene abnormalities were detected.

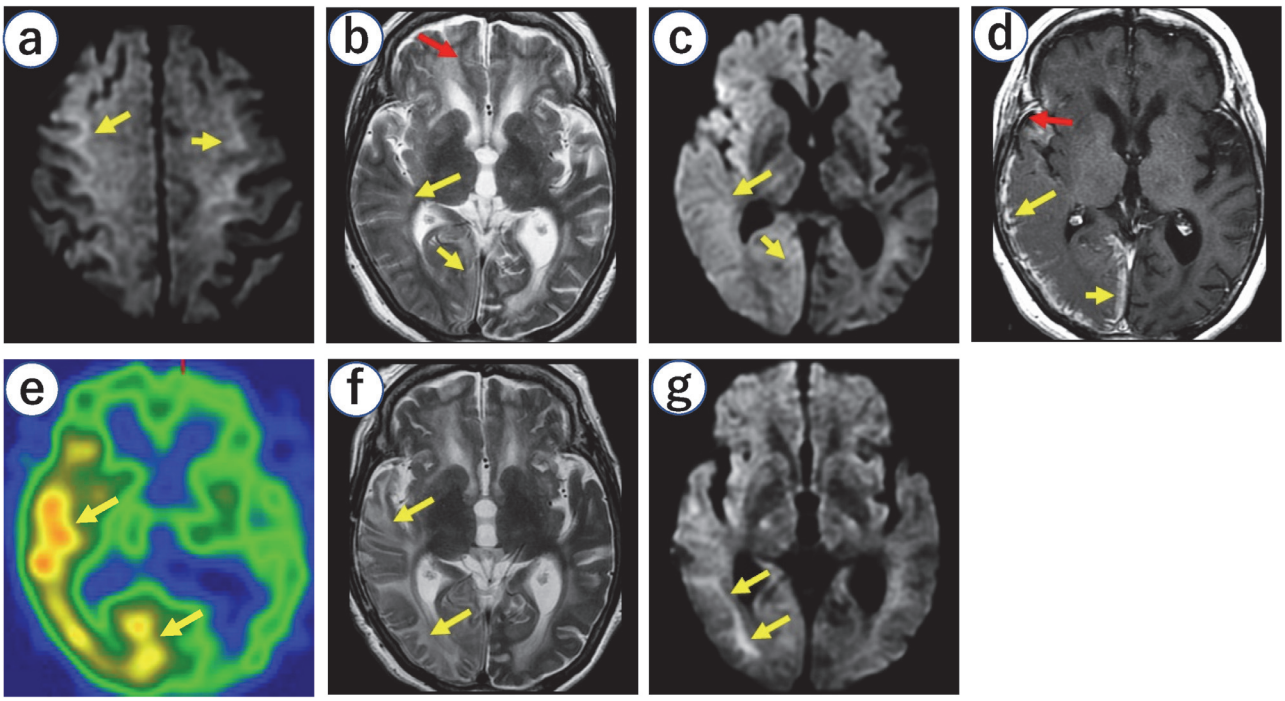

Fig. 1 – Magnetic resonance imaging. (A) Diffusion weighted images (DWI) images obtained at admission shows hyperintense lesions in the corticomedullary junctions (CMJs) of both frontoparietal lobes (yellow arrows). T2-weighted imaging (T2WI) (B) and DWI (C) obtained on day 15 of admission demonstrate swelling and hyperintensities in the cortices of the right temporal and occipital lobes (yellow arrows). The cortical sulci are effaced. Hyperintense lesions are seen bilaterally in the deep frontal white matter on T2WI (red arrows). Magnetic resonance angiogram demonstrates dilatation of the right middle cerebral artery and posterior cerebral artery (not shown). (D) T1-weighted image after administration of contrast medium shows cortical enhancement in the right temporal and occipital lobes (yellow arrows). Abnormal enhancement is mainly observed in the gyral crowns but absent or only slightly observed in the bottoms of sulci (crown enhancement). Abnormal enhancement is also seen in the dura mater adjacent to the cortices (red arrow). (E) SPECT image shows hyperperfusion in the right temporal and occipital lobes (yellow arrows). T2WI (F) and DWI (G) obtained on day 45 of admission show hyperintense lesions in the CMJs of the right temporal and occipital lobes (yellow arrows). Subcortical hyperintense lesions are also observed on T2WI but not in the corticies of the same areas. T2WI obtained 10 months later shows focal atrophy. Hyperintense lesions in the CMJs disappeared in the right temporal and occipital lobes as observed on DWI (not shown).

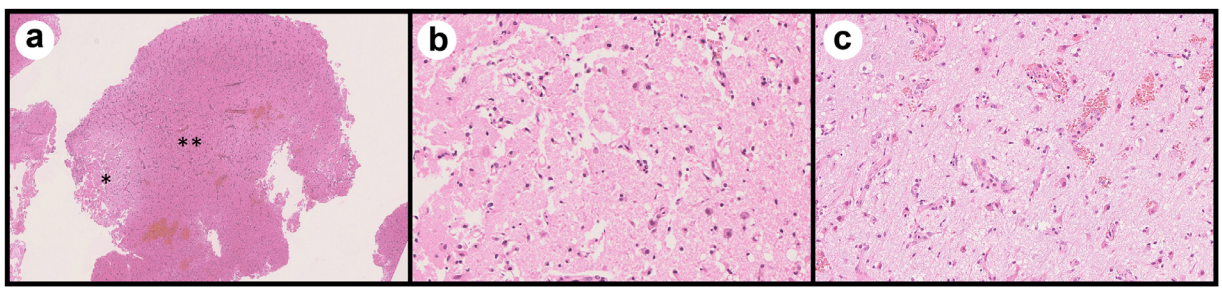

Fig. 2 – (H&E staining image). Biopsy showing a small, recent infarct in the cerebral cortex (*), continuous with which there was a lesion involving the deep cerebral cortex (**) (A). Recent infarct (*) showing parenchymal coagulative necrosis, extensive ischemic changes, and loss of the neurons, and mild endothelial swelling with cracking artifact of the section (B). The lesion continuous with a recent infarct and involving the deep cerebral cortex (**) was composed of edema, neuronal loss and ischemic changes, proliferation of the vessels with hypertrophic walls, and petechiae (C). Immunohistochemical analysis revealed numerous macrophages/microglia in the lesion (not shown).

Discussion

We present a case of NIID with subacute encephalopathy in which T2WIs showed cortical swelling and hyperintensities. In this case, infarctions were pathologically found in the deep cortical layers.

Sone et al. reported that 21% of adult-onset NIIDs had the characteristic symptoms of a subacute encephalitic episode, such as fever, headache, vomiting, and loss of consciousness [1]. Some papers report multiple episodes of encephalopathies during the course of the NIID [7–9]. Subacute encephalopathy of NIID is common in adult patients [1] but may also occur in young patients, such as in a case of a 19-year-old [10]. There are reports that steroid therapy was effective for encephalopathy symptoms, like reducing cerebral edema and improving the level of consciousness [1,9]. Our patient was also treated with steroids, and her encephalopathy symptoms gradually improved.

Common MRI findings in NIIDs with encephalopathy are hyperintensities and swelling in the cerebral cortices on T2WI [1,7,11]. Ataka et al. [12] described hyperperfusion in the abnormal corticies on technetium-99m ethyl cysteinate dimer SPECT, and Ishihara et al. [13] reported hyperperfusion on arterial spin labeling and dilation of the right cerebral arteries on magnetic resonance angiography. Previous studies have reported contrast enhancement in the abnormal cortices [1,9]. In our patient, abnormal enhancement was mainly observed in gyral crowns (ie, crown enhancement). Similarly, in a case presented by Sone et al. [1] and in 2 of the 4 cases in a study by Liang et al. [9], MR images showed strong enhancement in the gyral crowns. On the other hand, in the remaining 2 cases [9], contrast enhancement was observed in gyral crowns and bottoms of sulci [9].

MR images revealed changes in lesions over time in patients with subacute encephalopathy of NIID. According to previous reports [7,11], hyperintense lesions in the cortices on Fluid-attenuated inversion recovery (FLAIR) images were followed by lesions in the subcortical white matter and atrophy in the same area. However, no characteristic hyperintensities in the CMJs on DWI were observed. Okubo et al. [14] described 12 cases of NIID confirmed by genetic studies. The first DWI of 3 patients revealed no characteristic hyperintensities in the CMJs; however, subsequent DWI of both patients demonstrated characteristic hyperintensities. Furthermore, one patient had an episode of subacute encephalopathy 8 months after the initial MRI. In our patient, DWI and FLAIR images showed hyperintensities and swelling in the cerebral cortices in the right TOLs; however, the cortical lesions subsequently disappeared. Moreover, hyperintense lesions appeared in the subcortical white matter on FLAIR images, and hyperintense lesions appeared in the CMJs on DWI. Ten months later, hyperintensities in the CMJs on DWI disappeared. In one case [15], hyperintensities in the CMJs almost disappeared 5 years after the last hospitalization.

A principal target of the encephalopathy of NIID was the cortices [14]. In our patient, pathological examinations revealed new infarcts in the deep layers of the cortices and ischemic changes in the surrounding neurons. The findings obtained were not suggestive of encephalitis or vascular occlusions. Therefore, secondary degeneration might be responsible for the hyperintense lesions in the subcortical white matter; however, it remains unknown why the hyperintense lesions in the CMJs appeared on DWI after encephalopathy. Contrast enhancement was present in the dura mater adjacent to the cortices; such enhancements are generally not observed in ischemic lesions.

Characteristic hyperintense lesions in the CMJs are pathologically spongiotic changes [16,17]; however, there are few reports in which ischemic changes were found in the overlying cortices [17]. Characteristic hyperintense lesions of NIID on DWI are common in the CMJs of the frontoparietal lobes [1]; however, lesions in subacute encephalopathy are more common in the TOLs. Thus, some differences between characteristic hyperintense lesions of NIID and lesions after subacute encephalopathy of NIID have been observed.

Like the encephalopathy of NIID, cortical swelling and hyperperfusion are also observed in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) and postictal state.

Hyperperfusion in patients with MELAS is considered caused by increased oxygen and energy demands owing to neuronal hyperexcitability or hypoxia in tissues due to abnormal mitochondrial function, resulting in compensatory vasodilation [18]. There are reports in which subacute encephalopathy of NIID was misdiagnosed as MELAS [9,13]. However, in patients with MELAS, hyperintensities on DWI in the acute phase are distinct and extend to the cortices and subcortical white matter [19], whereas in patients with subacute encephalopathy of NIID, hyperintensities on DWI are absent or faint in the cortices and do not extend to the subcortical white matter. These are the most important distinctions between MELAS and subacute encephalopathy of NIID, which was consistent with those observed in our case. Neuronal hyperexcitability might be a cause of infarctions in subacute encephalopathy of NIID; however, its exact cause remains unknown.

The postictal state was reported to be accompanied by hyperperfusion and considered associated with prolonged neuronal hyperexcitability, thus causing changes in the cerebral cortex similar to those in hypoxic encephalopathy and inducing increased glucose levels and glucose metabolism in the brain and relative hypoxia [20]. Hyperintense lesions in the CMJs on DWI were not observed in the postictal state. Moreover, our patient did not have epilepsy.

Fragile X-related tremor and ataxia syndrome (FXTAS) is a disease with nuclear inclusion bodies similar to those found in NIID [2]. FXTAS differs from NIID in that no nuclear inclusion bodies are found in oligodendrocytes [21]. Pathological examinations of our patient revealed nuclear inclusion bodies in oligodendrocytes. Moreover, the MR images of patients with FXTAS showed lesions in the middle cerebellar peduncle with high frequency [22,23], which were not observed in our patient. Since genetic examinations for NIID or FXTAS were not performed, we were unable to completely exclude the possibility of FXTAS; however, to the best of our knowledge, there are no reports of FXTAS with encephalopathy accompanied by cortical swelling or enhancement.

In conclusion, NIID should be considered in the presence of the encephalopathy with cortical swelling, contrast enhance-

ment in the TOLs, and vasodilations in adult patients. The target of the encephalopathy was the cortices, and the pathological background included infarctions.

Ethical approval

This study was approved by our institutional ethical review board of Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital (approval no. 2757).

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Data availability

The underlying data can be accessed at reasonable request to the corresponding author.

Author contributions

Original draft preparation: Koichiro Mori; Writing - review and editing: Akira Yagishita, Nobuaki Funata, Ryoji Yamada, and Yasunobu Takaki.; Supervision: Yoshiharu Miura.

Patient consent

We obtained informed consent from the patient.

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