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Case Report

Non-convulsive status epilepticus associated with neuronal intranuclear inclusion disease: A case report and literature review

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ABSTRACT

We report a case of neuronal intranuclear inclusion disease (NIID) confirmed by detection of intranuclear inclusions in a skin biopsy specimen. Brain magnetic resonance imaging showed mild cerebral atrophy and linear hyperintensities at the corticomedullary junction on diffusion-weighted images. This patient developed nonconvulsive status epilepticus with generalized periodic discharges on electroencephalography after recurrent symptoms of paroxysmal nausea and slowly progressive cognitive decline. There have been no previous reports of NIID with nonconvulsive status epilepticus to our knowledge. Since adult patients with NIID display a wide variety of clinical manifestations, skin biopsy should be considered in patients who have leukoencephalopathy of unknown origin.

1. Introduction

Neuronal intranuclear inclusion disease (NIID) is a rare and slowly progressive neurodegenerative disease that has been reported as both sporadic and familial cases. The cardinal symptoms of NIID are slowly progressive dementia associated with parkinsonism, cerebellar ataxia, and peripheral neuropathy [1–3]. In addition, the disease is also associated with various types of seizures in adult and pediatric patients [2,3]. Immunohistochemical examination of biopsy specimens from the skin or subcutaneous abdominal fat was recently reported to be useful for diagnosis of NIID [4,5]. Case reports about patients with this disease have been gradually increasing, demonstrating considerable variation of its symptoms and clinical course [2,3]. However, genetic analysis for NIID or diagnostic criteria for this disease has not been established to date.

Non-convulsive status epilepticus (NCSE) presents with clinical signs such as unexplained changes in behavior and mental status, confusion, or even a severe tendency to sleep, accompanied by continuous epileptiform discharges in electroencephalography (EEG) [6,7], and is a critical condition that must be identified when managing patients with disturbance of consciousness. We encountered a patient with NIID who developed NCSE after presenting with recurrent paroxysmal nausea, slowly progressive cognitive decline, and loss of consciousness preceded by dizziness. To our knowledge, there have been no published reports of NCSE associated with NIID.

2. Case report

In June 2003, a 59-year-old Japanese woman presented with gradually worsening dysuria. Intermittent self-catheterization subsequently became necessary for retention of urine due to neurogenic bladder. Until April 2009, there were no particular problems with daily activities and she had no seizures, but there were several episodes of paroxysmal nausea and vomiting lasting for 2–3 days and slowly progressive cognitive decline was observed. In August 2010, she was admitted to our hospital. Her past medical history included hypothyroidism and retinal dystrophy. Her younger brother had recurrent encephalopathy of unknown etiology, but there were no neurological disorders among other family members and relatives. Neurological examination revealed mild impairment of memory, reduced sensation in the lower extremities, decreased tendon reflexes, and dysuria. Laboratory tests were normal, including the complete blood count, serum biochemistry, liver and renal function data, blood ammonia level, and cerebrospinal fluid parameters. EEG revealed 9 Hz alpha waves with intermittent delta waves in the bilateral frontal areas. Echocardiography, abdominal CT, and upper gastrointestinal endoscopy all showed normal findings. Myocardial scintigraphy using ^{123}I-metaiodobenzylguanidine demonstrated a marked decrease of cardiac uptake (heart/mediastinum ratio on delayed images was 1.49 [normal: ≥2.2] and washout rate was 59.6% [normal: ≤22]). Nerve conduction velocity studies revealed

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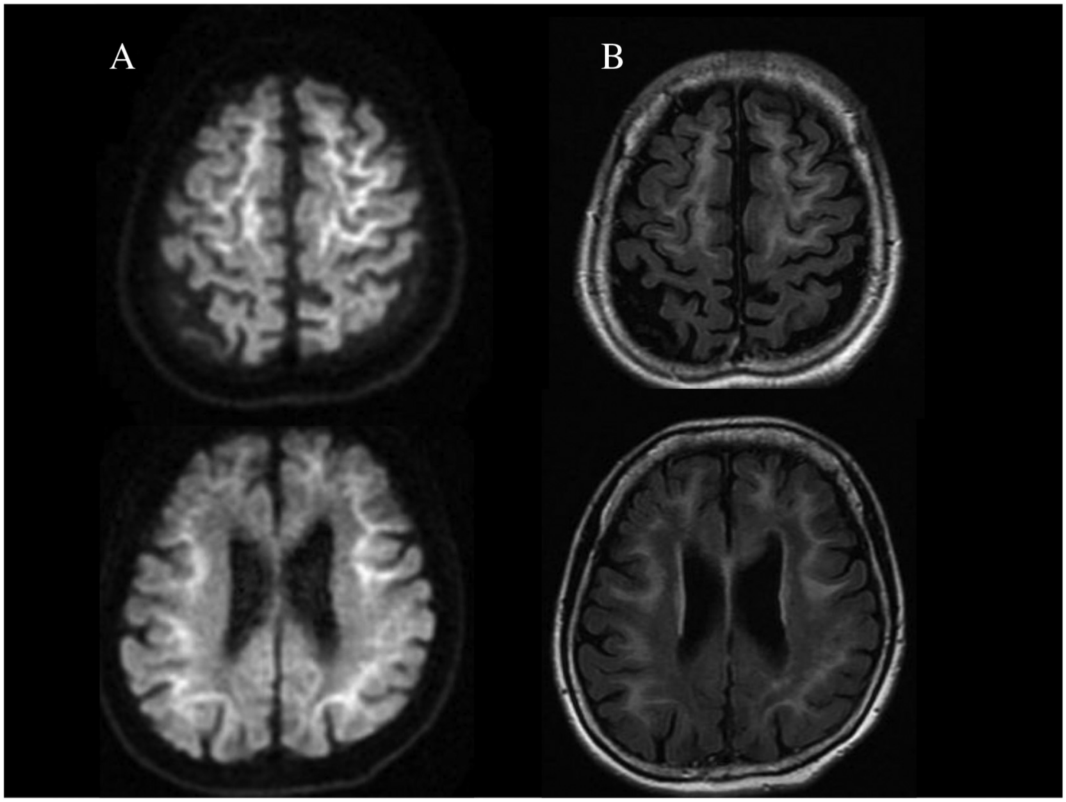

Fig. 1. Brain magnetic resonance imaging: diffusion weighted image (A) and fluid attenuated inversion recovery image (B). Slight brain atrophy is observed along with linear hyperintensities at the corticomedullary junction of the frontal and parietal lobes.

slightly delayed motor and sensory conduction. Brain magnetic resonance imaging (MRI) showed mild cerebral atrophy, with linear hyperintensities at the corticomedullary junction in the frontal and parietal lobes on diffusion-weighted and fluid-attenuated inversion recovery images (Fig. 1). A skin biopsy specimen was obtained from the right ankle, and intranuclear inclusions were detected by anti-ubiquitin immunostaining of fibroblasts, sweat gland cells, and adipocytes (Fig. 2).

NIID was diagnosed from these findings and the patient was discharged without medications. In October 2015, she developed

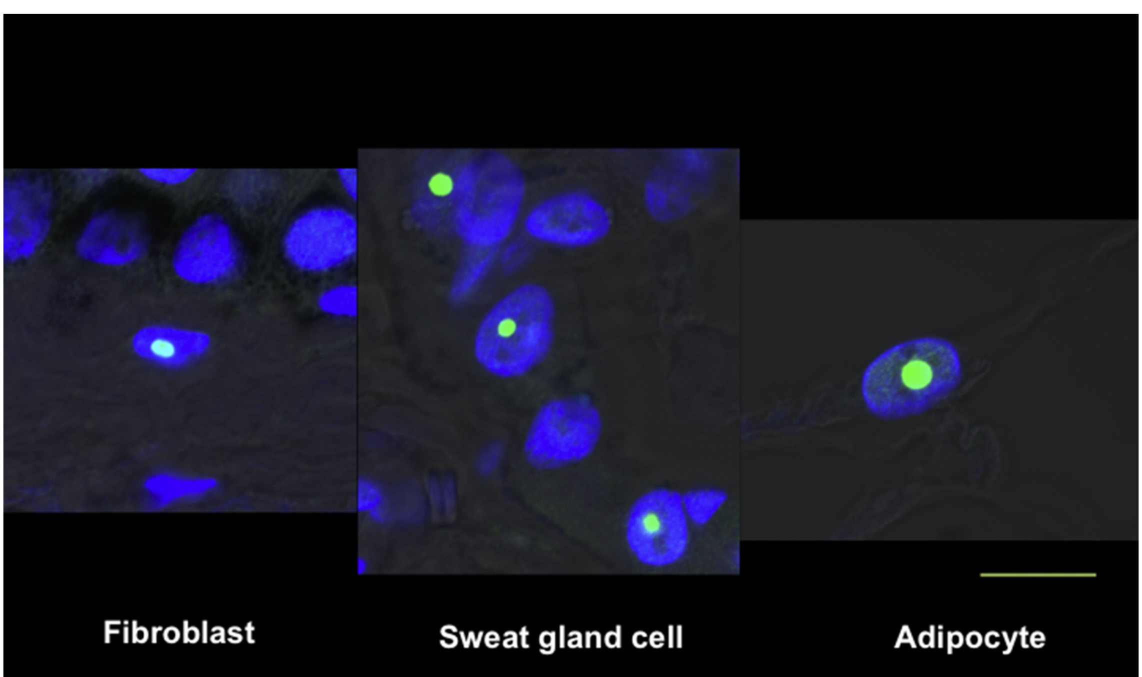

Fig. 2. Skin biopsy specimen. Immunofluorescence staining with anti-ubiquitin antibody and counterstaining with 4′, 6-diamidino-2-phenylindole di-lactate (DAPI). Intranuclear inclusions (arrows) are stained green by anti-ubiquitin antibody. The inclusions are located inside DAPI-positive (blue) nuclei in the merged view. Scale bar = 10 μm.

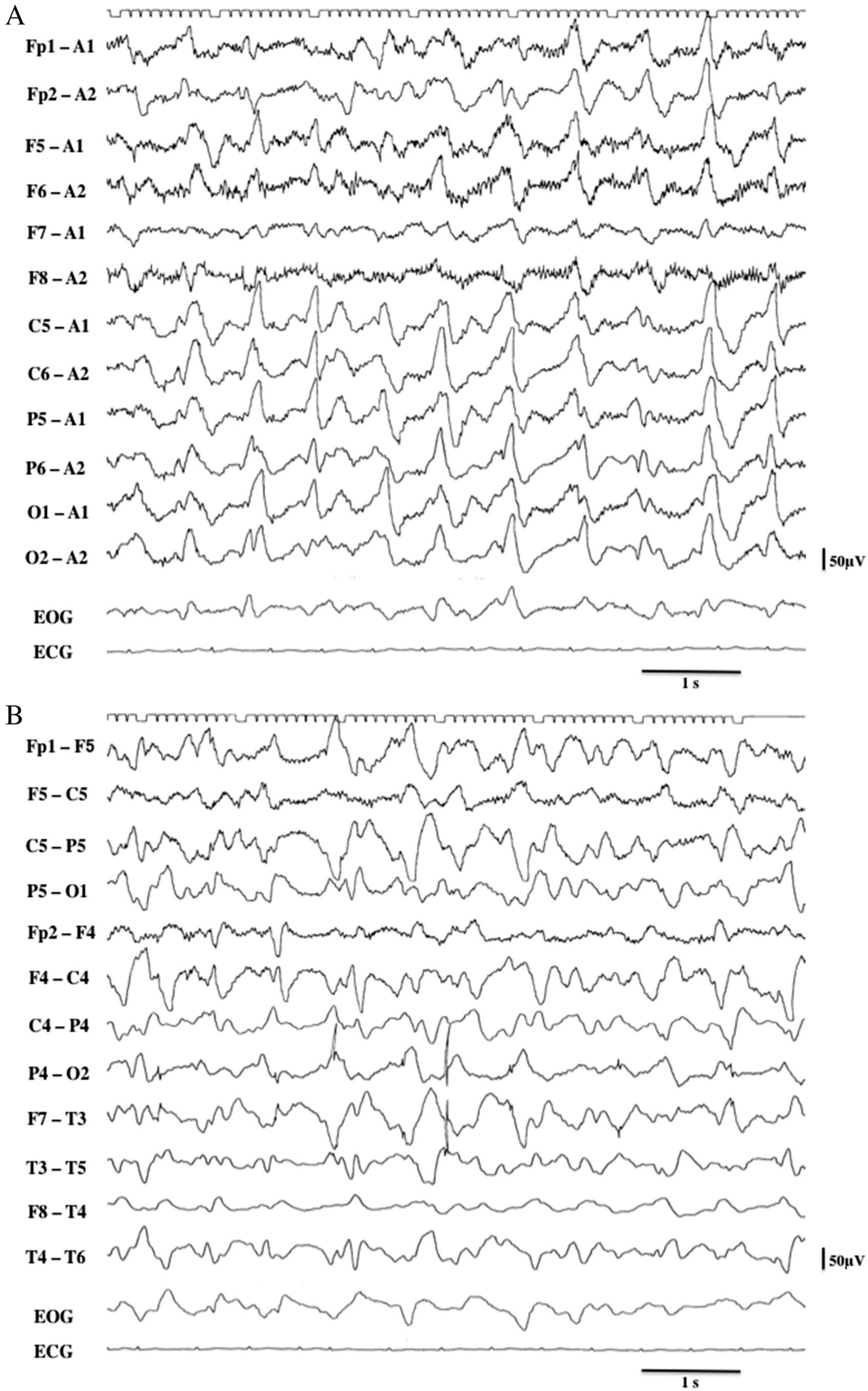

Fig. 3. EEG recorded at the second admission: a monopolar montage (A) and an A–P longitudinal bipolar montage (B). Although the patient was in a semi-comatose state without obvious motor signs suggesting a seizure involving her face or limbs, EEG exhibited generalized bilateral periodic delta waves and sharp waves with a high amplitude (80–150 μV) at intervals from 0.5 to 1 s, which were identified as generalized periodic discharges.

dizziness and vomiting, and was readmitted in a semi-comatose state. On the second hospital day, EEG revealed generalized bilateral high-amplitude periodic delta waves and sharp waves at 0.5–1 second intervals (Fig. 3), although no motor signs suggesting a seizure were noted. Intravenous phenytoin was administered and her consciousness improved to a clear state. After 2 weeks, she was discharged on oral anti-seizure medication. Although she could initially perform daily activities unaided, she died of aspiration pneumonia in another hospital after two years.

3. Discussion

Our patient manifested loss of consciousness without obvious convulsions, while EEG revealed generalized bilateral periodic delta waves and high-amplitude sharp waves at 0.5–1 second intervals, which were identified as generalized periodic discharges (GPDs). It was reported that periodic or rhythmic EEG abnormalities, such as GPDs, periodic lateralized epileptiform discharges, and triphasic waves, are frequent in patients with NCSE [6–8]. Since this case fulfilled the Salzburg consensus criteria for NCSE [9,10], we diagnosed NCSE featuring GPDs at 12 years after the onset of NIID.

Previously, NIID has been often diagnosed by post-mortem examination [1,2]. However, Sone et al. reported the usefulness of skin biopsy for diagnosing NIID in 2011 [4], after which a wide range of clinical manifestations have been demonstrated in patients with adult-onset NIID including cognitive impairment, pyramidal and extrapyramidal symptoms, cerebellar ataxia, neuropathy, and autonomic dysfunction [4,5]. With regard to epilepsy, seizure-like episodes such as recurrent syncope or falls have only been reported in six adults with NIID, although children with this disease often have seizures [1–3,11–13]. Espay et al. reported a 20-year-old woman with recurrent episodes of momentary loss of consciousness accompanied by mood changes, in whom EEG also demonstrated generalized periodic discharges [3]. In addition, Toyota et al. reported a 70-year-old woman with recurrent falls, in whom EEG revealed mid-temporal spikes and sharp waves [13], but there were no features of NCSE associated with GPDs like our case. In the other four patients with seizure-like episodes, EEG failed to confirm epileptic discharges [1,2,11,12]. Thus, we are not aware of previous reports involving a patient with NCSE and EEG confirmation of GPDs.

Hypoxic/anoxic encephalopathy was reported to be the most frequent cause of NCSE [6,7]. Although the etiology of NCSE with GPDs is unknown in our patient, it may have been related to cerebral hypoxia because the abnormalities we detected by diffusion-weighted MRI suggested cytotoxic edema like that frequently observed in ischemic stroke patients and recurrent stroke-like episodes have been reported in a patient with NIID [13]. Since progressive cognitive impairment may make it difficult to detect loss of consciousness due to NCSE in adult NIID patients, only a few previous reports of these patients have included EEG findings [4,13,14]. Accordingly, a diagnosis of NCSE may have been missed in some adult NIID patients with white matter lesions on MRI like those seen in the present case.

4. Conclusion

Previous reports have indicated a wide variety of clinical manifestations in adult NIID. We include NCSE in association with pathological examination of a skin biopsy specimen that may be helpful in patients with leukoencephalopathy showing dementia, parkinsonism, cerebellar ataxia, peripheral neuropathy, and autonomic failure of unknown origin.

Ethical statement

Informed consent was obtained from the patient and family.

Conflicts of interest

The authors have no conflicts of interest to report.

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