



## Perfusion abnormality in neuronal intranuclear inclusion disease with stroke-like episode: A case report

Fumiya Kutsuna<sup>a,b</sup>, Yohei Tateishi<sup>a,\*</sup>, Kairi Yamashita<sup>a</sup>, Tadashi Kanamoto<sup>a</sup>, Takuro Hirayama<sup>a</sup>, Tomoaki Shima<sup>a</sup>, Atsushi Nagaoka<sup>a</sup>, Shunsuke Yoshimura<sup>a</sup>, Teiichiro Miyazaki<sup>a</sup>, Jun Sone<sup>c,d</sup>, Tsuyoshi Izumo<sup>e</sup>, Akira Tsujino<sup>a</sup>

<sup>a</sup> Department of Neurology and Strokeology, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan

<sup>b</sup> Department of Neurology, National Hospital Organization Nagasaki Medical Center, 2-1001-1 Kubara, Omura, Nagasaki, 856-0835, Japan

<sup>c</sup> Department of Neurology, National Hospital Organization Suzuka National Hospital, 3-2-1 Kasado, Suzuka, 513-8501, Mie, Japan

<sup>d</sup> Department of Neuropathology, Institute for Medical Science of Aging, Aichi Medical University, 1-1 Yazakokarimata, Nagakute, Aichi, 480-1195, Japan

<sup>e</sup> Department of Neurosurgery, Nagasaki University Hospital, 1-7-1 Sakamoto, Nagasaki, 852-8501, Japan

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### ABSTRACT

Neuronal intranuclear inclusion disease (NIID) is a slowly progressive neurodegenerative disease. Some patients with NIID occasionally present with acute symptoms. However, its mechanism remains unclear. We report a patient with NIID who presented with a stroke-like episode. Arterial spin labeling magnetic resonance imaging revealed hypoperfusion in the focal cerebral region at the onset while no apparent arterial occlusion was observed. The abnormal perfusion area was normalized 6 days after admission. Therefore, the perfusion abnormality was likely the main cause of acute neurologic deficits in NIID. NIID should be considered in the differential diagnosis of stroke mimics.

### 1. Introduction

Neuronal intranuclear inclusion disease (NIID) is a neurodegenerative disease which is characterized by eosinophilic hyaline intranuclear inclusions in the central and peripheral nervous system, as well as in other tissues [1]. The number of patients diagnosed with NIID has increased in recent years due to the establishment of skin biopsy. Although NIID generally follows a slowly progressive course, which is accompanied by numerous symptoms, some cases have suggested that the patient with NIID occasionally experiences acute manifestations including stroke-like episodes [2]. Cerebral perfusion changes may provoke the acute manifestations with NIID [2,3]. However, it remains debatable. Herein, we report the case of NIID with a stroke-like episode accompanied by cerebral blood flow changes.

### 2. Case report

A 63-year-old man who had a 15-year history of urinary retention

followed by staggering gait presented to the emergency room of our hospital because of abrupt onset of speech disturbance and dysgraphia. He had a medical history of hypertension and diabetes. There was no history of alcohol intake and no family history of neurological disorder. Speech disturbance and dysgraphia had disappeared on arrival at our hospital. The duration of these symptoms was approximately two hours. Neurologic examination revealed bilateral miosis, paresthesia, reduced tendon reflexes of the bilateral lower extremities, ataxic gait with wide base, and a positive Romberg test. Diffusion-weighted imaging revealed linear hyperintensity lesions in the white matter adjacent to the cerebral cortex (Fig. 1a), and those were isointense on apparent diffusion coefficient. Fluid-attenuated inversion recovery imaging revealed diffuse bilateral white matter hyperintensity (Fig. 1b). In addition, hypoperfusion of the left temporal lobe was identified on arterial spin labeling (ASL) (Fig. 1c). Magnetic resonance angiography revealed no occlusive lesion in major intracranial cerebral artery (Fig. 1d).

We considered that transient ischemic attack was the main pathophysiology of this patient and suspected that NIID accidentally existed

\* Corresponding author at: 1-7-1 Sakamoto, Nagasaki City, Nagasaki 852-8501, Japan.

E-mail addresses: [ytate@nagasaki-u.ac.jp](mailto:ytate@nagasaki-u.ac.jp) (Y. Tateishi), [kairiy@nagasaki-u.ac.jp](mailto:kairiy@nagasaki-u.ac.jp) (K. Yamashita), [tadashik@nagasaki-u.ac.jp](mailto:tadashik@nagasaki-u.ac.jp) (T. Kanamoto), [t-hirayama@nagasaki-u.ac.jp](mailto:t-hirayama@nagasaki-u.ac.jp) (T. Hirayama), [tomoakishima0915@nagasaki-u.ac.jp](mailto:tomoakishima0915@nagasaki-u.ac.jp) (T. Shima), [a-naga@nagasaki-u.ac.jp](mailto:a-naga@nagasaki-u.ac.jp) (A. Nagaoka), [shun-yoshimura@nagasaki-u.ac.jp](mailto:shun-yoshimura@nagasaki-u.ac.jp) (S. Yoshimura), [tmiyazaki@nagasaki-u.ac.jp](mailto:tmiyazaki@nagasaki-u.ac.jp) (T. Miyazaki), [sone.jun.nq@mail.hosp.go.jp](mailto:sone.jun.nq@mail.hosp.go.jp) (J. Sone), [tizumo@nagasaki-u.ac.jp](mailto:tizumo@nagasaki-u.ac.jp) (T. Izumo), [akrtjn@nagasaki-u.ac.jp](mailto:akrtjn@nagasaki-u.ac.jp) (A. Tsujino).

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based on the typical features of his medical history, symptoms, and magnetic resonance imaging (MRI) findings. Laboratory tests and the cerebrospinal fluid study revealed no abnormality including lactate/pyruvate ratio of cerebrospinal fluid. Neither Holter electrocardiography monitoring, transthoracic echocardiography, nor duplex ultrasonography of the carotid artery identified any possible embolic source of ischemic stroke. Although the score of the Mini-Mental State Examination was 28 (normal threshold, 24/30), Frontal Assessment Battery score was 11, which was lower than the threshold of 16/18. Electroencephalogram showed no epileptic discharge. Nerve conduction study showed a mild reduction in both motor and sensory nerve conduction velocity. Fragile X-associated tremor/ataxia syndrome was ruled out since the genetic testing for the fragile X chromosome mental retardation gene 1 (*FMR1*) revealed no CGG premutation. Although the analysis of the NOTCH2NLC gene mutation was performed, the patient did not expect the disclosure of whether the genetic mutation existed or not. A histopathological examination of skin biopsy specimens showed eosinophilic hyaline intranuclear inclusions in the sweat gland cells and adipocytes in the dermal layer. He was diagnosed with NIID because of characteristic MRI and pathological findings. Follow-up ASL (Fig. 1e) and N-isopropyl-p-[<sup>123</sup>I] iodoamphetamine (<sup>123</sup>I-IMP) single-photon emission computed tomography (SPECT) conducted at six days from admission revealed no evidence of perfusion abnormality (Fig. 1f). No significant temporal changes were seen in major intracranial cerebral artery between initial and the follow-up MRAs. There was no evidence of embolic sources and no occlusion or stenosis of artery. Nevertheless, ASL revealed cerebral blood flow changes. We considered that the stroke-like episodes may be attributed to the pathophysiology of NIID. He was discharged without any neurological sequelae.

### 3. Discussion

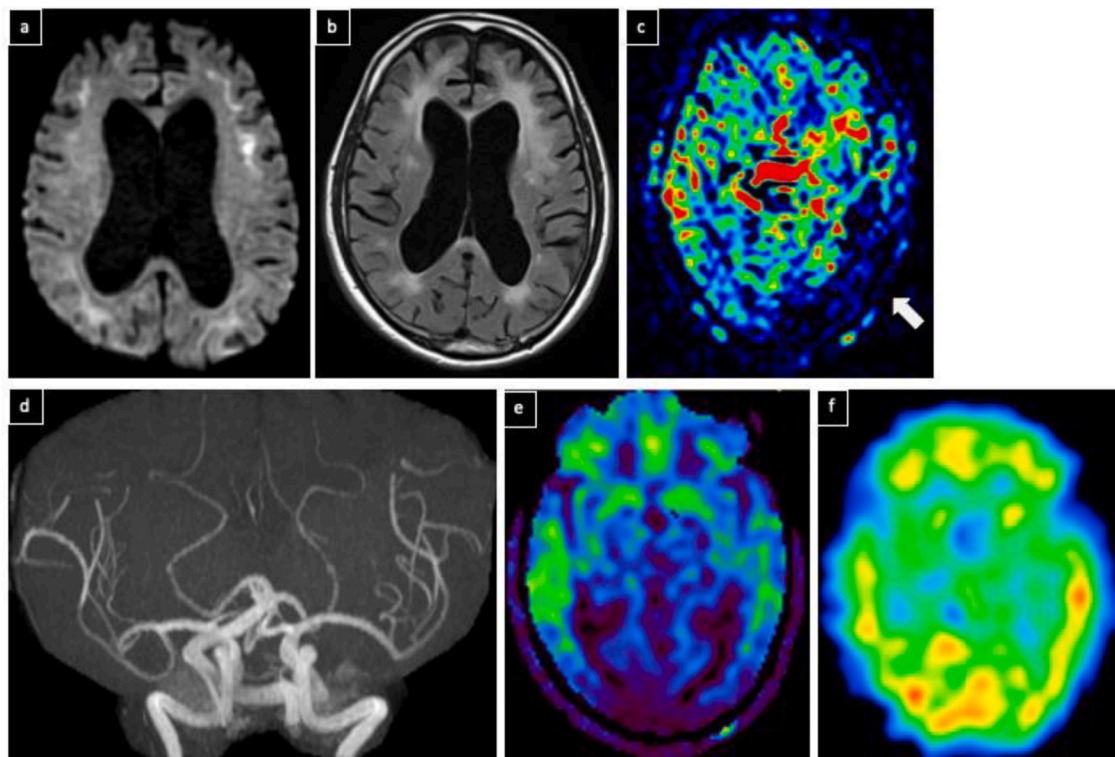
We report a patient with NIID who presented with a stroke-like

episode. ASL detected the temporal change of the cerebral perfusion in the focal lesion. The acute episode of this patient could be attributed to hypoperfusion detected at admission.

Patients with NIID is generally have chronic manifestations, such as dementia, ataxia, and bladder and bowel dysfunction, which shows gradual progression [1]. However, some patients with NIID occasionally experience acute episodes [2]. In a previous report, a patient experienced transient attacks of acute symptoms, which were aphasia and right hemiparesis during the first instance and headache, left spatial neglect, and left hemiparesis during the second episode [2]. Perfusion images including ASL and <sup>123</sup>I-IMP-SPECT revealed hypoperfusion at the onset and hyperperfusion afterward in each episode. In our case, ASL revealed hypoperfusion in the left temporal lobe at the acute phase, and ASL and <sup>123</sup>I-IMP SPECT after six days of onset detected no cerebral perfusion changes. Although hypoperfusion in the chronic phase of sporadic and familial NIID could be common [1], the mechanism of acute manifestations in patients with NIID remains unclear. Acute manifestations in cases with NIID could be attributed to decreased cerebral perfusion.

The unsolved issue remains how NIID evokes cerebral perfusion changes. Patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) present similar cerebral blood flow changes due to mitochondria angiopathy. A patient with NIID was seen to have MELAS-like symptoms and images [4]. A previous biopsy case report revealed the accumulation of eosinophilic inclusions in the vascular smooth muscles [5]. The accumulation of eosinophilic inclusions in cerebrovascular smooth muscle cells may play a critical role in vascular dysfunction which led to cerebral perfusion changes in patients with NIID.

We eventually recognized that this patient's stroke-like symptoms were attributed to the acute episode of NIID because of the typical features of his history and MRI findings. However, some patients with NIID did not have hyperintensity of the corticomedullary junction in



**Fig. 1.** Neuro-radiological findings. a) Diffusion-weighted imaging reveals the high intensity lesions in the corticomedullary junction of the bilateral hemispheres. b) Fluid-attenuated inversion recovery imaging reveals diffuse high-intensity signal of white matter. c) Arterial spin labeling at the onset shows hypoperfusion in the left hemisphere (arrow). d) Magnetic resonance angiography reveals no significant intracranial arterial occlusive lesions. e) Arterial spin labeling and f) N-isopropyl-p-[<sup>123</sup>I] iodoamphetamine single-photon emission computed tomography at six days after the admission reveals no apparent hemodynamic changes.

DWI, which is characteristic of NIID, especially in the early phase of the disease course [3,4]. Moreover, patients with NIID who have a hypoperfusion area in the focal cerebral region could be misdiagnosed as having ischemic stroke. The acute episode of NIID should be included as the differential diagnosis of stroke mimics.

#### 4. Conclusion

We reported a patient with NIID who developed a stroke-like episode accompanied by dynamic perfusion changes on ASL. Acute neurological deficits in NIID could be caused by perfusion abnormality. This case may emphasize the importance of recognizing NIID as stroke mimics.

#### Declaration of Competing Interest

None.

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#### Author contributions

Fumiya Kutsuna: Conceptualization, Writing – Original Draft, Visualization. Yohei Tateishi: Writing – Review and Editing. Kairi Yamashita, Tadashi Kanamoto, Takuro Hirayama, Tomoaki Shima, Atsushi

Nagaoka, Shunsuke Yoshimura, and Teiichiro Miyazaki: Visualization, Investigation. Jun Sone: Resources. Tsuyoshi Izumo: Validation. Akira Tsujino: Supervision.

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