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Letter to the Editor

Neuronal intranuclear inclusion disease showing blepharoptosis and positive serum anti-acetylcholine receptor antibody without myasthenia gravis

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Dear Editor,

Neuronal intranuclear inclusion disease (NIID) is a slowly progressive neurodegenerative disease, pathologically characterized by eosinophilic hyaline intranuclear inclusions in the central and peripheral nervous systems as well as in visceral organs [1,2]. Clinically, NIID presents with various neurological manifestations, including dementia, autonomic impairment, peripheral neuropathies, abnormal behavior, and disturbed consciousness [1]. Magnetic resonance imaging (MRI) findings are characteristic, showing high-intensity signals along the corticomedullary junction on diffusion-weighted images (DWI) [2]. Recently, skin biopsy is used for diagnosis of NIID [3,4].

Anti-acetylcholine receptor antibody (AChR-Ab) is a specific marker for myasthenia gravis (MG) [5]. To date, there have been no reports of NIID with elevated serum AChR-Ab or blepharoptosis. Herein, we report a patient with NIID showing blepharoptosis and positve serum AChR-Ab without MG.

1. Case presentation

A 61-year-old man, who had diabetes mellitus, hypertension, and hyperlipidemia for several years, consulted our hospital. The patient had bilateral blepharoptosis since 40-year-old (Fig. 1A–C) and weakness in the lower-extremities since 60-year-old, without easy muscle fatigue or diurnal variation of muscle weakness. He had no family history of neurological disorders. The blepharoptosis became gradually worse. Neurological examinations showed bilateral blepharoptosis, miosis, mildly limited eye movement in all directions, mild weakness of bilateral orbicularis oculi, areflexia in extremities, mild atrophies/weaknesses of both proximal and distal muscles in four extremities, and waddling gait. The patient presented with no nystagmus, sensory disturbance, or urinary disturbance. Tests for cognitive functions were normal; Mini-Mental State Examination (MMSE): 30 points, Wechsler Adult Intelligence Scale III (WAIS III): full-scale IQ 122, and Wechsler Memory Scale–Revised (WMS-R): general memory 122. Blood examinations were normal, except for elevated serum creatine kinase (CK; 520 IU/mL; cut off < 250 IU/L) and AChR-Ab (5.8 pmol/mL; cut off < 0.2 pmol/L). Cerebrospinal fluid (CSF) examinations showed mildly elevated protein (60 mg/dL, normal < 40 mg/dL) without pleocytosis. Chest computed tomography (CT) showed no evidence for thymoma or thymic hypertrophy. Nerve conduction studies showed diffuse slowing of conduction velocities in both the motor and sensory nerves in the extremities. The patient had no evidence of MG, since repetitive nerve stimulation test did not show waning, and blepharoptosis was not improved by edrophonium or ice tests. Aerobic exercise tests showed normal pattern for lactate and pyruvic acid. Brain MRI showed high-intensity in the corticomedullary junction on DWI and in the bilateral cerebral white matter on T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) (Fig. 1D–E). The brain MRI showed no chronological change for high-intensity lesions on DWI or T2-FLAIR for 2 years after the initial examination. Orbital MRI revealed thinning of all extraocular muscles (Fig. 1F). Leg T1-weighted MRI showed hyperintensity in the bilateral gastrocnemius (Fig. 1G). Muscle biopsy from the left gastrocnemius revealed infiltration of fatty tissues with extensive perimysial and endomysial fibrosis, as well as variation of muscle fiber size and the presence of central nuclei (Fig. 1H). ATPase staining revealed that both type I and II fibers were involved, and that there was no fiber type grouping. No intranuclear inclusion bodies (IIBs) were found in the muscle specimens. However, abdominal skin biopsy revealed eosinophilic IIBs positive for anti-ubiquitin and anti-p62 antibodies in the sweat glands and fibroblasts (Fig. 1I–K). IIBs were not found in adipocytes for all the specimens.

2. Discussion

Our patient developed blepharoptosis since 40-year-old, followed by lower-extremity weakness at 60-year-old. Neurophysiological, imaging, and pathological studies revealed both myopathy and neuropathy. Cognitive functions were preserved. The MRI findings and IIBs in the skin led to the diagnosis of NIID. Interestingly, although serum AChR-Ab was positive, there were no myasthenic symptoms or neurophysiological evidence for MG, despite ocular manifestations including ptosis and ophthalmoplegia. Based on the muscle biopsy findings and negative evidence of MG, we considered that these ocular manifestations seemed

Abbreviations: AChR-Ab, anti-acetylcholine receptor antibody; NIID, neuronal intranuclear inclusion disease; IIBs, intranuclear inclusion bodies

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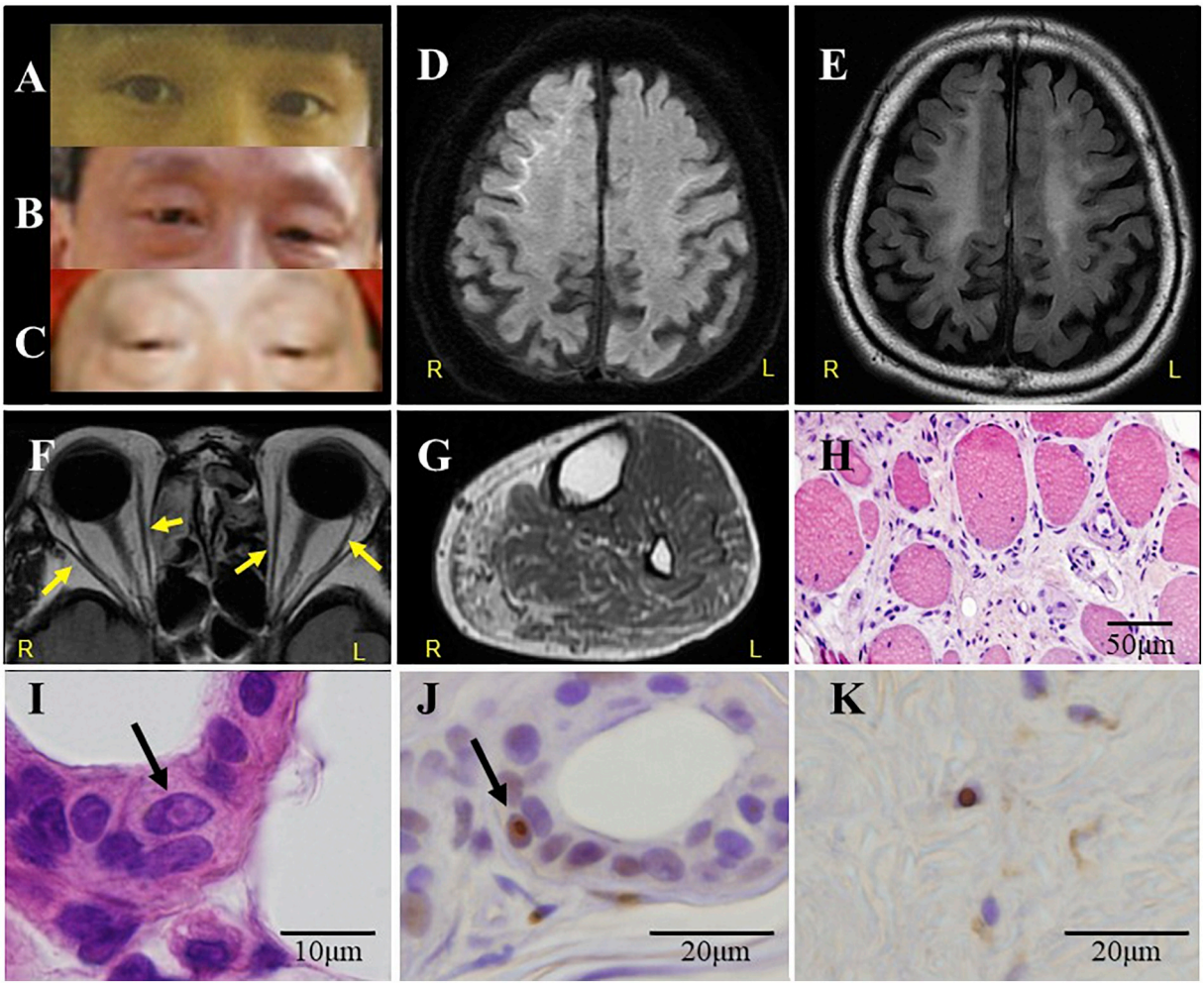

Fig. 1. A–C: The transition of blepharoptosis: age of 25 (A), 43 (B), and 60 years (C). D–E: Brain MRI showing hyperintensity in the corticomedullary junction on diffusion-weighted imaging (DWI) (D) and in the bilateral cerebral white matter on T2-weighted fluid-attenuated inversion recovery (FLAIR) (E). F: T1-weighted MRI showing the thinned extraocular muscles (yellow arrows). G: T1-weighted MRI of the left leg, showing high intensity diffusely in the gastrocnemius muscle. H: Muscle biopsy from the gastrocnemius muscle showing infiltration of fatty tissues, with extensive perimysial and endomysial fibrosis and variation of muscle fiber size. I: In the skin biopsy, eosinophilic intranuclear inclusions were found in the sweat gland cell (black arrow). J-K: Intranuclear inclusion bodies are positive for immunolabeling against ubiquitin (black arrow) (J) and p62 (K). (I, sweat gland H&E; J, sweat gland, anti-ubiquitin antibody; K, fibroblast, anti-p62 antibody). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to be caused by ocular myopathy, and that the origins of the ocular symptoms are related to NIID, although we could not have direct evidence for it.

To date, there have been no reports of patients with NIID presenting blepharoptosis, ophthalmoplegia, or elevated AChR-Ab mimicking MG. As the specificity of AChR-Ab was 95–100% in MG [5], AChR-Ab is a reliable marker for the diagnosis of MG. Although we could not find any normal control subjects with elevated serum AChR-Ab in the literature, a high serum AChR-Ab titer was reported in thymoma without MG [6]. However, these cases could develop myasthenic symptoms within several years [6]. It is reported that elevated serum AChR-Ab, myasthenic symptoms, or other forms of evidence for MG, including responsiveness to edrophonium test, were seen in other neuromuscular diseases, such as amyotrophic lateral sclerosis, myotonic dystrophy, limb-girdle muscular dystrophy, facioscapulohumeral muscular dystrophy, and chronic progressive external ophthalmoplegia [7,8]. Mechanisms of positive AChR-Ab in these neuromuscular disorders remain unclear, although autoimmune reactions against neurodegeneration or muscle fiber damage were speculated in genetic myopathies and motor neuron disease [7,8]. We could not determine the reason for elevated AChR-Ab in our case, but we speculate that the antibody is produced by immune response against neurodegeneration or muscle fiber damage. However, the reason why our patient did not develop myasthenic symptoms, despite elevated serum AChR-Ab, remains unclear; we speculate that differences in the antibody recognition site of AChR prevented the appearance of myasthenic symptoms.

Myopathy is a rare phenotype of NIID, but two cases were reported previously. One patient was a 30-year-old man with NIID who had proximal dominant myopathy in four extremities and bulbar signs such as a nasal voice, dysarthria, and dysphagia. Muscle biopsy revealed rimmed vacuoles-like inclusion body myopathy and IIBs in the nuclei of the cells, but myofilament structure was not identified within the cytoplasm of inclusion-bearing cells [9]. The other patient with NIID, who died at 9-year-old, had suffered from incoordination, gait disturbance, aphasia, head ptosis, athetosis, drooling and cardiomegaly; IIBs were found in the cardiomyocytes, but not in the skeletal muscle [10]. Clinical manifestations in our patient were distinct from those in the two patients described previously.

In conclusion, we report the first case of NIID showing blepharoptosis and AChR-Ab positivity without evidence of MG, requiring further investigation to reveal the underlying pathophysiology.

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Disclosure of conflict of interest

None.

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