


Corticobasal Syndrome in a Patient with Anti-IgLON5 Antibodies

Kimiharu Fuseya, MD, Akio Kimura, MD, Nobuaki Yoshikura, MD, Megumi Yamada, MD, Yuichi Hayashi, MD, and Takayoshi Shimohata, MD, PhD* 

Anti-IgLON5 disease is a novel neurological disorder characterized by disturbed sleep, bulbar dysfunction, movement disorders, oculomotor abnormalities, and cognitive impairment.^{1,2} Neuropathological findings have also revealed tauopathy.³ No reports have described patients with anti-IgLON5 antibodies that presented with corticobasal syndrome (CBS). Here, we report the first such case of CBS in a patient with anti-IgLON5 disease.

Case Report

A 78-year-old woman with a 4-year history of slowly progressive left-sided impaired dexterity and gait disturbance was identified. Upon admission, neurological examination showed rigidity, dystonia in the lower left limb, left-sided apraxia, cortical sensory deficit, and gait disturbance (Video S1). This patient showed no oculomotor abnormalities, cognitive impairment, or bulbar dysfunction. Although she had mild insomnia and obstructive sleep apnea (apnea hypopnea index on polysomnography, 11.6), this patient did not experience excessive daytime sleepiness or vocal cord palsy during laryngoscopy. The polysomnography demonstrated no abnormal sleep architecture or stridor, which were all confirmed by a sleep expert certified by the Japanese Society of Sleep Research. In addition, we and a floor nurse did not observe her parasomnia during the course of hospitalization. She was diagnosed with probable corticobasal degeneration (clinical phenotype; probable CBS) based on the consensus criteria for its diagnosis proposed by Armstrong and colleagues.⁴ Anti-IgLON5 antibodies were detected in serum, but not in cerebrospinal fluid, at a titer of 1:100 by immunofluorescence on human embryonic kidney cells transfected with a full-length IgLON5 plasmid (Fig. 1A–D). The immunohistochemical results using frozen rat cerebellar sections are similar to those of previous reports¹ (Fig. 1E). This patient was a carrier of the *HLADRB1*01:01* and *HLADQB1*05:01* alleles. Brain

magnetic resonance imaging revealed cortical atrophy, predominantly in the right parietal lobe (Fig. 1F,G). ¹²³I-N-isopropyl-p-iodoamphetamine (IMP) single-photon emission computed tomography (SPECT) showed a reduction of tracer uptake in the right parietal cortex (Fig. 1H). Dopamine-transporter (DAT) SPECT showed a reduction of tracer uptake in the bilateral striatum (specific binding ratio by the bolt method [SBR]_{Bolt}; right, 1.39; left, 2.22)⁵ (Fig. 1I). Her striatal SBR was well below the lower limit of age-matched healthy Japanese controls because the lower limit of the 95% prediction interval is 4.41.⁶ The patient was then treated with intravenous methylprednisolone pulse therapy for 3 days followed by 2 courses of intravenous immunoglobulin (IVIG) therapy for 5 days. A few weeks after IVIG therapy, her apraxia, gait disturbance, and cortical sensory deficits gradually improved. She could put on her left shoe and turn over in bed with ease and walk with less assistance from the caregiver. The IMP SPECT and DAT scans were repeated 41 days and 33 days after IVIG therapy, respectively. The uptake of tracer during IMP SPECT and DAT SPECT (SBR_{Bolt}; right, 2.40; left, 3.56) was also significantly improved. At the present time (9 months after intravenous methylprednisolone pulse therapy), the patient's apraxia and cortical sensory deficits are continuing to improve. However, her gait disturbance gradually returned. She was therefore treated with 1 additional course of IVIG therapy and is continuing to improve.

Discussion

To our knowledge, this is the first case report of a patient with anti-IgLON5 disease presenting with CBS that meets the diagnostic criteria of probable corticobasal degeneration. Our study revealed 2 key findings. First, we discovered that the occurrence of CBS in the setting of the anti-IgLON5 disease is expanding the clinical spectrum of this disease, although the complete

Department of Neurology, Gifu University Graduate School of Medicine, Gifu, Japan

*Correspondence to: Dr. Takayoshi Shimohata, Department of Neurology, Gifu University Graduate School of Medicine, Gifu, 1-1 Yanagido, Gifu 501-1194, Japan; E-mail: shimohata@gmail.com

Keywords: Parkinson's disease, dystonia, tremor, parkinsonism, tics.

Relevant disclosures and conflicts of interest are listed at the end of this article.

Received 8 February 2020; revised 2 April 2020; accepted 6 April 2020.

Published online 5 May 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.12957

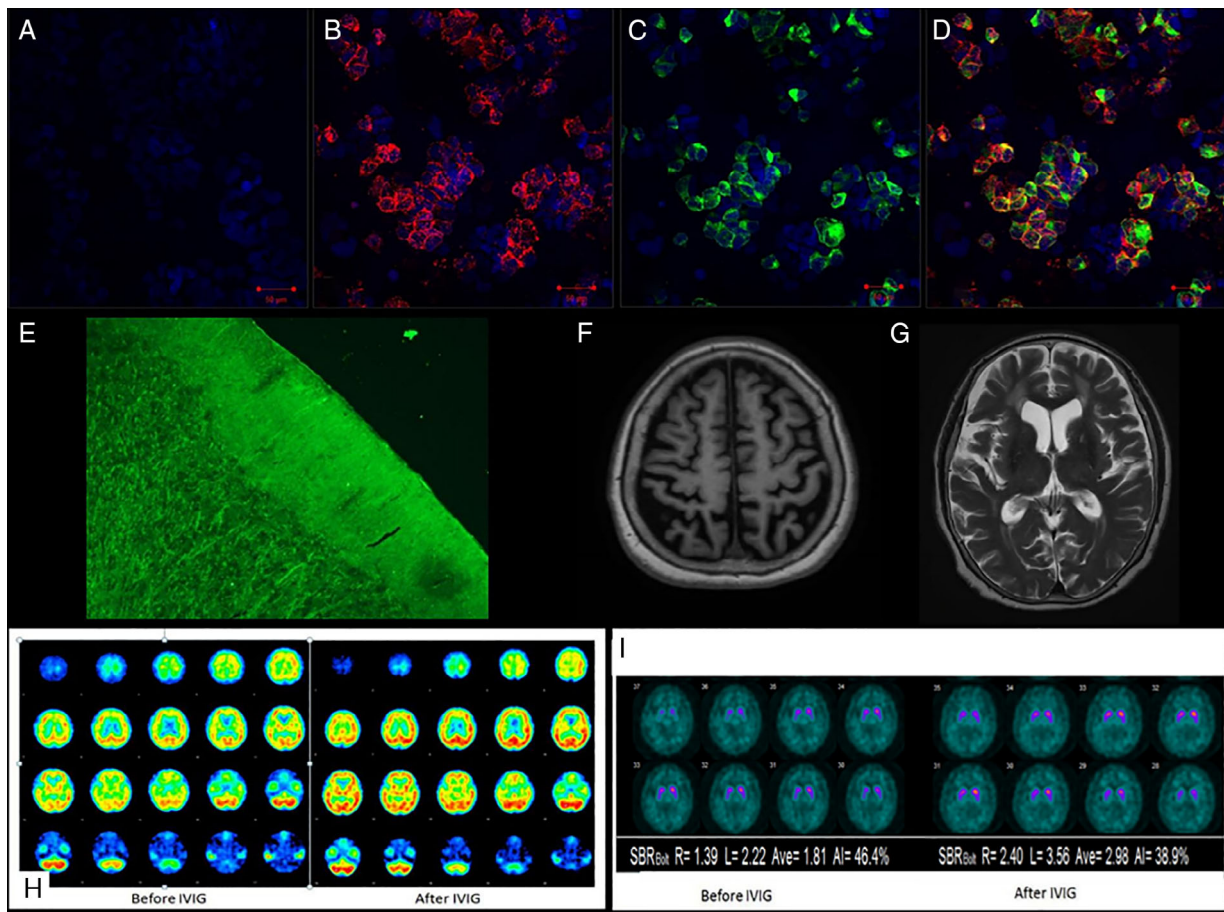


FIG. 1. Cell-based assay of full-length IgLON5-transfected human embryonic kidney 293 cells (A–D). The human embryonic kidney 293 cells stably express green fluorescent protein–tagged IgLON5 (C). Anti-IgLON5 antibodies were detected in the patient's sera (B), but not in the healthy control's sera (A). Colocalization of the patient's immunoglobulin G and IgLON5 is yellow in merged images (D). DNA is stained with 4,6-diamidino-2-phenylindole (blue). Tissue-based immunofluorescence assay using frozen rat cerebellar sections is shown (E). Immunoreactivity is particularly robust in the cerebellum for which there is diffuse labelling of the molecular layer and synaptic glomerula of the granular layer. Brain magnetic resonance imaging revealed cortical atrophy predominantly in the right parietal lobe (F), and no abnormal findings of the bilateral striatum (G). ^{123}I -N-isopropyl-p-iodoamphetamine single-photon emission computed tomography showed a reduction of tracer uptake in the parietal cortex (H). After IVIG therapy, it showed an increase of tracer uptake in the bilateral cortex, especially the parietal cortex (H). Dopamine-transporter single-photon emission computed tomography showed a reduction of tracer uptake in the bilateral striatum (I). After IVIG therapy, it showed an increase of tracer uptake in the bilateral striatum (I). AI, asymmetry index; AVE, average; IVIG, intravenous immunoglobulin; L, left; R, right; SBR_{Bolt}, specific binding ratio by the bolt method.

background of this patient's pathology remains unknown. Second, we showed the effectiveness of immunotherapy in this patient, confirmed both clinically and by radioisotope assessments (IMP SPECT, DAT SPECT). This case highlights the importance of testing for anti-IgLON5 antibodies in patients with CBS who could potentially benefit from immunotherapy.

Acknowledgment

We thank Mrs. Eri Sakai for technical assistance.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

K.F.: 1A, 1B, 1C, 2A, 2B

A.K.: 1A, 1B, 1C, 2A, 2B

N.Y.: 1B, 1C, 2B

M.Y.: 1B, 2B

Y.H.: 1B, 2B

T.S.: 1A, 1B, 1C, 2A, 2B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. Written informed consent was obtained from the patient for publication of this case report. We also confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: The authors report no sources of funding and no conflicts of interest.

Financial Disclosures for previous 12 months: The authors declare that there are no additional disclosures to report.

References

1. Sabater L, Gaig C, Gelpi E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol* 2014;13:575–586.
2. Gaig C, Graus F, Compta Y, et al. Clinical manifestations of the anti-IgLON5 disease. *Neurology* 2017;2:1736–1743.
3. Gelpi E, Höftberger R, Graus F, et al. Neuropathological criteria of anti-IgLON5-related tauopathy. *Acta Neuropathol* 2016;4:531–543.
4. Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. *Neurology* 2013;5:496–503.
5. Tossici-Bolt L, Hoffmann S, Kemp P, et al. Quantification of [123I]FP-CIT SPECT brain images: an accurate technique for measurement of the specific binding ratio. *Eur J Nucl Med* 2006;33:1491–1499.
6. Matsuda H, Murata M, Mukai Y, et al. Japanese multicenter database of healthy controls for [123I]FP-CIT SPECT. *Eur J Nucl Med Mol Imaging* 2018;45:1405–1416.

Supporting Information

Supporting information may be found in the online version of this article.

Video S1 The patient's eye movement was normal. She showed apraxia in the left upper extremity. She had dystonia in the left lower extremity and also had difficulty in putting on her left shoes because of left-sided apraxia. She showed gait disturbance with wide-based and short step gait. After treatment, apraxia in her left upper extremity was improved and she could put on her left shoe with ease and walk with a straight back.