Case report

Autoimmune basal ganglia encephalitis associated with anti-recoverin antibodies: A case report

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ARTICLE INFO

Keywords:
Autoimmune basal ganglia encephalitis
Parkinsonism
Autoimmune encephalitis
High-dose immunoglobulin
Anti-recoverin antibodies

ABSTRACT

Autoimmune basal ganglia encephalitis causes neurological symptoms such as parkinsonism associated with basal ganglia lesions. Here, we report a case of autoimmune basal ganglia encephalitis without retinal lesions or malignancy harboring anti-recoverin antibodies. The patient was a 67-year-old Japanese woman who developed anorexia, parkinsonism, and disturbance of consciousness 7 days before admission. Brain magnetic resonance imaging showed hyperintense bilateral basal ganglia lesions on fluid-attenuated inversion recovery images. 18F-fluorodeoxyglucose-positron emission tomography showed no malignancy in the trunk, and dopamine transporter single-photon emission computed tomography with dopamine transporters revealed reduced radiotracer uptake in the basal ganglia. Further, anti-recoverin IgG antibodies were detected in serum immunoblot. Based on the clinical and imaging findings, the patient was diagnosed with autoimmune basal ganglia encephalitis with anti-recoverin antibodies and administered high-dose immunoglobulins (HD-IVIG), which led to an improvement in clinical symptoms. Anti-recoverin antibodies are paraneoplastic antibodies that explicitly bind to Ca" binding proteins in the retina and cause retinopathy. This pathological sequence is defined as cancer-associated retinopathy (CAR). However, in our case, autoimmune basal ganglia encephalitis developed without CAR syndrome or malignancy. Clinicians should be aware of the possibility of autoimmune basal ganglia encephalitis showing anti-recoverin antibodies but no CAR syndrome or malignancy, which should be treated with HD-IVIG therapy.

1. Introduction

Autoimmune basal ganglia encephalitis is a spectrum of autoimmune basal ganglia disorders in which patients develop neurological symptoms of parkinsonism, including involuntary movements, rigidity, and tremors associated with basal ganglia lesions [1]. Usually, autoantibodies against the dopamine D2 receptor (D2R) and N-methyl-D-aspartate receptor (NMDAR) [1,2] have been associated with the development of autoimmune basal ganglia encephalitis.

Anti-recoverin antibodies (Abs) are paraneoplastic Abs that bind to specific retinal Ca" binding proteins leading to retinopathy [3]. Herein, we report a case of autoimmune basal ganglia encephalitis that harbored anti-recoverin Abs without retinal lesions or malignancy.

2. Case report

A 67-year-old healthy Japanese woman was admitted to a local hospital for anorexia, rigidity, and multiple arthralgia (pain in four or more joints in the body) of the extremities that lasted for approximately a week. On the first day after admission, blood tests showed a normal white blood cell count (4.600/μL), normal electrolytes and glucose levels, and elevated regular C-reactive protein (CRP) levels (8.3 mg/dL; normal range, <0.3 mg/dL). On day 2, brain magnetic resonance imaging (MRI) showed a hyperintense lesion in the right caudate nucleus on diffusion-weighted imaging (DWI) and lesions in the bilateral basal ganglia on fluid-attenuated inversion recovery imaging (FLAIR) and T2-weighted imaging (WI) (Fig. 1A-C). T1-WI, T2 star-WI, and brain computed tomography (CT) showed right basal ganglia calcification but

https://doi.org/10.1016/j.ensci.2021.100382
Received 27 August 2021; Received in revised form 25 September 2021; Accepted 17 November 2021
Available online 24 November 2021
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no hemorrhagic lesions (Fig. 1D–F).

On day 2, the patient presented with fever, somnolence, and parkinsonism (resting tremor and rigidity in her extremities consistent with classic Parkinson’s disease). Nasopharyngeal swab was negative for SARS-CoV-2 on a reverse transcription-polymerase chain reaction (PCR) assay. She showed no signs of meningeal irritation on day 2 and no lumbar puncture was performed. Contrast-enhanced CT of the trunk showed no findings suggestive of infection. $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG)-positron emission tomography (PET)-CT showed $^{18}$F-FDG accumulation in the bilateral basal ganglia lesions, with no accumulation in the trunk on day 5 (Fig. 2A, B). The patient’s somnolence and Parkinson’s symptoms progressed, and the fever became prolonged. As examinations of Parkinson’s symptoms, dopamine transporter (DAT) single-photon emission computed tomography (SPECT) revealed reduced radiotracer uptake in the basal ganglia on day 38 (Fig. 2C). $^{123}$I-metiodobenzylguanidine (MIBG) myocardial scintigraphy showed no reduction in myocardial uptake (early phase, 2.33; delayed phase, 2.32; normal range, >2.2; washout rate, 24.8%; normal range, <30%, based on facility references); therefore, Parkinson’s disease was discarded on day 41 (Fig. 2D). The patient had multiple arthralgia (symmetrical shoulders, neck, and thighs) and met the diagnostic criteria of the European League Against Rheumatism/American College of Rheumatology for polymyalgia rheumatica (PMR); therefore, the patient was diagnosed with PMR. On day 42, as initial treatment, she was treated with prednisolone (PSL) (15 mg/day) for PMR and L-dopa/decarboxylase inhibitor (L-dopa/DCI) 100 mg/day for Parkinson’s syndrome. Although the fever and CRP levels improved after PSL administration, the patient became less responsive to stimuli and the psychological and neurological symptoms including somnolence, lethargy, and parkinsonism gradually worsened despite treatment on day 56. Therefore, PMR was ruled out as the patient’s clinical condition. She progressed from somnolence to coma and was referred to our hospital (University of Fukui, Fukui, Japan) on day 66.

On admission, the neurological examination revealed a disturbance in consciousness (Glasgow Coma Scale [GCS] 5; E2V1M2) and severe parkinsonism, including persistent rigidity and akinesia with an inability to walk. The patient was in stable respiratory condition and did not require tracheal intubation or ventilator management. Therefore, she was differentiated with catatonia, a psychiatric symptom for disturbed consciousness. Blood tests revealed elevated white blood cells (9.600/μL) and normal CRP levels (0.3 mg/dL). Serological Abs against nuclear, thyroid peroxidase, thyroglobulin, glutamic acid decarboxylase, aquaporin 4, and D2R were all negative. Screening for autoimmune encephalitis with Abs against neuron surface antigens (autoantibodies to NMDAR, AMPAR, GABA$_\alpha$R, GABA$_\beta$R, mGluRs 1, 2, and 5, DPPX, IgLON5, LGI1, and CASPR2) yielded negative results in both serum and cerebrospinal fluid (CSF). In the search for anti-neuronal Abs, a serum immunoblot (BML Co. Ltd., Tokyo, Japan) was strong positive (3+) for anti-recoverin Abs. Other anti-neuronal Abs (amphiphysin, CV2/CRMP-5, PNMA2 (Ma2/Ta), Ri, Yo, Hu, SOX1, titin, zic4, and Tr (DNER)) were negative in the serum. CSF examination revealed pleocytosis (30/μL, 100% lymphocytes) and normal protein levels, and a normal CSF IgG index. CSF culture and herpes simplex virus (HSV)-PCR were negative, ruling out infectious encephalitis. The oligoclonal band

![Fig. 1. Brain magnetic resonance image (MRI) (A–E) and computed tomography (CT) (F) of the patient on day 2. (A) Diffusion-weighted image (DWI; 3.0 Tesla; b value = 1000 s/mm$^2$; TR, 7000 ms; TE, 74.2 ms; axial) showing hyperintensity in the right caudate nucleus. (B) Fluid-attenuated inversion recovery image (FLAIR; 3.0 Tesla; TR, 10,000 ms; TE, 118.7 ms; axial) showing a hyperintensity lesion in the bilateral basal ganglia. (C) T2-weighted image (T2-WI; 3.0 Tesla; TR, 4841 ms; TE, 87.6 ms; coronal) showing a hyperintensity lesion in the bilateral basal ganglia. (D) T1-weighted image (T1-WI; 3.0 Tesla; TR, 2483 ms; TE, 18.9 ms; axial) showing calcification of the right basal ganglia. (E) T2 star-weighted image (T2 star–WI; 3.0 Tesla; TR, 550 ms; TE, 18.0 ms; axial) showing no hemorrhagic lesions. (F) Brain CT (axial) showing low density in the right caudate nucleus and no hemorrhagic lesions. Abbreviations: CT: Computed tomography, DWI: diffusion-weighted imaging, FLAIR: Fluid-attenuated inversion recovery imaging, MRI: Magnetic resonance imaging, WI: weighted image.](image-url)
on arterial spin labeling (ASL)-MRI on day 86 and N-isopropyl-p-123I-iodoamphetamine (123IIMP)-SPECT on day 107 showed no hyper-perfusion in the basal ganglia lesions. Abbreviations: ASL: arterial spin labeling, CT: Computed tomography, DAT: Dopamine transporter, DWI: diffusion-weighted imaging, 18F-FDG: 18F-fluorodeoxyglucose, FLAIR: Fluid-attenuated inversion recovery imaging, MIBG: 123I-meta-iodobenzylguanidine, MRI: Magnetic resonance imaging, 123IIMP: N-isopropyl-p-123I-iodoamphetamine, PET: Positron emission tomography, SPECT: single-photon emission computed tomography, WI: weighted image.

3. Discussion

Herein, we report a case of autoimmune basal ganglia encephalitis with anti-recoverin Abs without retinal lesions or malignancy. Key considerations were 1) whether anti-recoverin Abs were involved in autoimmune basal ganglia encephalitis and 2) whether HD-IVIg therapy was appropriate for treatment.

Autoimmune basal ganglia encephalitis is an autoimmune basal ganglia disorder, such as Sydenham’s chorea, which presents with movement disorders associated with basal ganglia lesions [1]. In 2012, anti-D2R Abs, neuronal surface antigen Abs, were reported to be involved in the pathogenesis of autoimmune basal ganglia encephalitis [1]. In a previous report, 71% (n = 12/17) of these encephalitis cases had serum anti-D2R Abs, which were completely undetectable in the healthy group (n = 0/67) [1]. Patients with autoimmune basal ganglia encephalitis and anti-D2R Abs developed movement disorders, such as dystonia and parkinsonism, as well as psychiatric symptoms such as anxiety and sleep disorders [1]. Some of these cases with anti-D2R Abs showed CSF pleocytosis (25%), slow EEG waves (42%), and basal ganglia lesions on MRI (50%) [1], all consistent with our case. In particular, in the present case, the patient with anti-recoverin Abs had a broader phenotype, such as somnolence and a decrease in responsiveness in addition to parkinsonism, which was not consistent with simple basal ganglia pathology. Further, imaging of the limbic system in the present case showed normal findings, and limbic encephalitis was not involved as a cause of the patient’s psychiatric symptoms. In past reports, patients with autoimmune basal ganglia encephalitis who showed basal ganglia atrophy or gliosis on acute scans had persistent impairment of cognitive and psychiatric functions [1]. Our patient also had imaging abnormalities in the basal ganglia region in the acute phase, which may have led to the development of her psychiatric disorders, including somnolence and catatonia. Furthermore, despite the lack of DAT-SPECT reports on dopaminergic denervation in autoimmune basal ganglia encephalitis, our case showed reduced radiotracer uptake in the basal ganglia due to basal ganglia lesions. DAT-SPECT findings in the present case showed hypoperfusion in the basal ganglia lesions. DAT-SPECT findings in the present case showed reduced radiotracer uptake in the basal ganglia due to basal ganglia lesions. DAT-SPECT findings in the present case showed reduced radiotracer uptake in the basal ganglia due to basal ganglia lesions.
Anti-NMDAR Abs and anti-neuronal surface Abs have been detected in other autoimmune basal ganglia encephalitis cases. Five percent of autoimmune encephalitis cases with anti-NMDAR Abs develop basal ganglia lesions [2]. Another autoimmune basal ganglia encephalitis case had serum anti-Yo and anti-CV2/CRMP-5 Abs, which are paraneoplastic anti-intracellular Abs [4]. However, none of these were detectable in the serum and CSF of our patient; only serum anti-recoverin Abs were detected.

As mentioned, anti-recoverin Abs are paraneoplastic Abs that bind to specific retinal Ca$^{2+}$-binding proteins leading to retinopathy [3]. Recoverin is mainly expressed by malignant tumors such as small cell lung cancer and breast cancer, and Abs against recoverin cross-react with photoreceptors. As a result, suppression of recoverin function by these Abs disrupts photoreceptor light signaling mechanisms, resulting in retinal degeneration [3]. This pathological sequence is defined as cancer-associated retinopathy (CAR) [3]. However, not all patients with anti-recoverin Abs develop CAR syndrome [3]. Also, anti-recoverin Abs can be detected in the serum of patients without malignancy [3]. In our patient, autoimmune basal ganglia encephalitis with anti-recoverin Abs developed without CAR syndrome or lung cancer as background of this antibody production. In past, two anti-recoverin Ab-positive cases with central nervous system (CNS) symptoms such as cerebellar ataxia have been reported [5,6]. One of the cases was associated with malignancy and developed retinopathy [5], while the other case was not associated with malignancy or retinopathy [6], as in our case (Table 1).

Next, we discuss the relationship between anti-recoverin Abs and CNS involvement in autoimmune basal ganglia encephalitis. For instance, patients with ocular toxoplasmosis also have progressive retinal or CNS symptoms due to anti-recoverin Abs [7]. Furthermore, recoverin shares epitopes with CNS endogenous antigens; therefore, anti-recoverin Abs that reach the CNS via the blood-brain barrier could show cross-reactivity within the CNS [7]. In the CNS, neuron-specific Ca$^{2+}$-binding protein neuronal cells in the caudate-putamen mainly express hippocalin [8], which shows 51% sequence similarity with recoverin [9]. Therefore, the present case could have been triggered by cross-reactivity between hippocalin and anti-recoverin Abs in the bilateral caudate nuclei and putamen, leading to autoimmune basal ganglia encephalitis. Basal ganglia tissue immunofluorescence assay after incubation with the patient’s CSF was not performed, and the background immunological mechanism underlying the symptoms lacked further support.

Anti-recoverin Abs are often detected in the serum after infections such as toxoplasmosis, and one of the initial symptoms of our patient was a fever, which differentiated post-infectious immune-mediated basal ganglia encephalitis. One of the mechanisms of entry of anti-recoverin Abs into the CNS was a direct route via the blood.[3], which was influenced by systemic inflammation [7]. However, the patient had no prior infection. In addition, the initial fever was accompanied by rigidity of the extremities and psychiatric symptoms such as somnolence and lethargy during the same period. Therefore, the initial fever in the patient might have developed due to hypothalamic dysfunction caused by encephalitis, not immune-mediated basal ganglia encephalitis after infection.

In our patient, both neurological symptoms and basal ganglia lesions significantly improved after HD-IVIG therapy. In 9 of 12 CAR syndrome cases with anti-recoverin Abs there was stabilization of visual symptoms after HD-IVIG therapy [10]. HD-IVIG therapy for patients with anti-recoverin Abs was mainly administered in combination with other treatments, such as steroids, rituximab, and plasmapheresis [10]. Past case reports of anti-recoverin Ab-positive patients with CNS symptoms showed that while steroid monotherapy was not effective [5], a combination therapy of steroids, HD-IVIG, and rituximab improved neurological symptoms of the patient [6] (Table 1). Our patient dramatically improved after HD-IVIG therapy, while there were no effects with PSL administration alone. The bilateral basal ganglia showed hyperintensity on FLAIR images and normal rCBF perfusion on ASL-MRI and 123IIMP-SPECT after HD-IVIG therapy. The improvement in these imaging findings was consistent with her clinical course. Our report suggests that HD-IVIG therapy is effective even in basal ganglia encephalitis with anti-recoverin Abs but no CAR syndrome. Further studies with larger sample sizes and longer post-immunotherapy follow-up are needed to corroborate our finding.

### 4. Conclusion

Clinicians should be aware of the possibility of autoimmune basal ganglia encephalitis showing anti-recoverin Abs without CAR syndrome or malignancy and should consider administering HD-IVIG therapy.

### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Human studies

Informed consent was obtained from the patient and her caregiver. The 1964 Declaration of Helsinki and later versions were followed in the conduct and writing of this case report.

### Declaration of Competing Interest

None.

### Table 1

Clinical findings of anti-recoverin antibody-positive cases with CNS symptoms [5,6] in comparison with the present case.

| Classification                  | Ryu et al. [5]                          | Herzog et al. [6]                          | Present case                   |
|---------------------------------|----------------------------------------|-------------------------------------------|--------------------------------|
| Sex                             | Male                                    | Female                                    | Female                         |
| Age                             | 65                                      | 60±                                       | 67                             |
| Malignancy                      | + (Small cell lung cancer)               | −                                        | −                              |
| Movement disorder               | −                                       | −                                        | −                              |
| Parkinsonism                    | +                                       | +                                        | +                              |
| Ataxia                          | −                                       | −                                        | −                              |
| Psychiatric symptoms            | −                                       | −                                        | −                              |
| Retinopathy                     | +                                       | −                                        | −                              |
| Antibody assay method           | Immunoblot                              | Cell-based assay                          | Immunoblot                     |
| Other Abs                       | + (Anti-Hu)                             | −                                        | −                              |
| MRI abnormal                    | + (Leukoaraiosis)                       | + (Cerebellar atrophy)                    | + (Bilateral basal ganglia)    |
| CSF abnormal                    | + (Pleocytosis)                         | −                                        | + (Pleocytosis)                |
| EEG epileptic changes           | −                                       | n.d.                                     | −                              |
| Treatment                       | −                                       | −                                        | −                              |
| Steroid                         | +                                       | +                                        | +                              |
| HD-IVIG                         | −                                       | −                                        | −                              |
| Rituximab                       | −                                       | +                                        | +                              |
| Outcome                         | No response                             | Improve                                  | Improve                        |

Abbreviations: Abs: Antibodies, CSF: Cerebrospinal fluid, EEG: Electroencephalogram, HD-IVIG: High-dose immunoglobulin, MRI: Magnetic resonance imaging.
Acknowledgments

None.

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