

Neurological Autoimmunity Associated With Homer-3 Antibody

A Case Series From China

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Abstract

Background and Objective

To present 6 new cases with Homer-3 antibodies that expand their clinical spectra and to evaluate the effect of immunotherapy.

Methods

Patients with suspected autoimmune cerebellar disorder were tested for rare autoimmune cerebellar ataxia (ACA) antibodies (anti-Tr(DNER)/Zic4/ITPR1/Homer-3/NCDN/PKC γ /PCA-2/AP3B2/mGluR1/ATP1A3 antibodies) using both cell-based and tissue-based assays. Patients with positive serum or CSF results who were diagnosed with ACA were registered and followed up. This study reports and analyzes cases with Homer-3 antibodies.

Results

Of the serum and CSF samples of 750 patients tested, 6 were positive for Homer-3 antibodies. All manifested subacute or insidious-onset cerebellar ataxia. Furthermore, 2 patients each exhibited encephalopathy, myeloradiculopathy, REM sleep behavior disorder, and autonomic dysfunction. Brain magnetic resonance images were normal ($n = 1$) or revealed cerebellar atrophy ($n = 1$), cerebellum and pons atrophy with the hot cross bun sign ($n = 2$), and bilateral cerebral abnormalities ($n = 2$). Definite leukocytosis was identified in the CSF of 2 patients, protein concentration elevation was observed in the CSF of 1 patient, and oligoclonal bands were present in 2 patients. All patients received immunotherapy, including corticosteroid, IV immunoglobulin, plasma exchange, and mycophenolate mofetil, after which the residual disability was still severe (modified Rankin Scale score ≥ 3 at the last follow-up in 4 patients and final Scale for the Assessment and Rating of Ataxia scores of 12–29), although 4 patients partially improved and 1 patient stabilized. The remaining 1 patient continued to deteriorate after repeated immunotherapy. Two patients relapsed.

Discussion

Disorders associated with Homer-3 antibody can mimic multiple system atrophy with cerebellar features in both clinical and radiologic aspects. Accurate identification of autoimmune-mediated cases is critical. Timely, comprehensive immunotherapy is warranted, given the possibility of long-term clinical benefit.

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Glossary

ACA = autoimmune cerebellar ataxia; **RBD** = REM sleep behavior disorder; **MSA-C** = multiple system atrophy with cerebellar features; **IVIg** = IV immunoglobulin.

Autoimmune cerebellar ataxia (ACA) comprises a considerable proportion of subacute cerebellar dysfunction.¹ The autoimmune process can be triggered by heterogeneous factors including infection, systemic malignancy, or hypersensitivity (such as gluten intolerance); it might also be idiopathic.² In some patients, antineuronal autoantibodies can be detected in the serum and CSF. While most autoantibodies binding to the extracellular domain are directly pathogenic, those targeting intracellular proteins are generally believed to be non-pathogenic, although they may serve as markers of immune-mediated mechanisms.³ Thus far, approximately 20 antibodies to cerebellar antigens have been detected, most of which bind to intracellular structures of Purkinje cells, including anti-Hu, anti-Yo, and anti-Homer 3.^{4,5}

Immunotherapy might be effective in ACA patients with autoantibodies targeting intracellular antigens, usually when the treatment is initiated soon after symptom onset.⁶

In this study, we present 6 patients with Homer-3 antibodies manifested as cerebellar ataxia with or without encephalopathy, REM sleep behavior disorder (RBD), encephalopathy, and radiculopathy. Their clinical characteristics and treatment responses are reported, together with a literature review of this condition.

Methods

Patients

Between January 2016 and December 2020, the Neuroimmunology and Encephalitis Laboratory of our hospital tested serum and CSF samples of 750 patients with clinically suspected autoimmune cerebellar disorders for an additional panel of ACA antibodies (anti-Tr(DNER)/Zic4/ITPR1/Homer-3/NCDN/PKC γ /PCA-2/AP3B2/mGluR1/ATP1A3 antibodies) using both cell-based and tissue-based assays (EUROIMMUN, Lübeck, Germany), as previously reported.⁷ From the overall cohort, we identified 6 patients who had Homer-3 antibodies in their serum or CSF. Three of the 6 patients were admitted to our hospital; the other 3 were evaluated at external neurologic centers, and their serum and CSF samples were sent to our laboratory. One of the patients from our hospital has been previously reported.⁷

Clinical Information and Follow-up

For these patients, clinical data, brain MRI, blood samples, and CSF were evaluated. Spinal MRI, sleep monitoring and electrophysiology workups, including EMG, nerve conduction studies, and EEG were also conducted if clinically warranted. We examined the complete blood count and

biochemical tests and screened for infection, toxins, and metabolic and systemic autoimmune diseases. The assays also included CSF cell counts, glucose and protein concentrations, and oligoclonal bands. Serum and CSF paraneoplastic antibody assays (anti-Hu/Yo/Ri/Ma2/Ta/CV2/amphiphysin antibodies), autoimmune encephalitis antibodies (anti-NMDAR/LGII/GABAb/CASPR2/GAD65/IgLON5/DPPX antibodies), and antibodies against aquaporin protein-4 and gangliosides were also examined. Serum antiglutin IgG/IgA and genetic testing using a hereditary ataxia panel (evaluating spinocerebellar ataxia genes [SCA 1, 2, 3, 6, 7, 8, 10, 12, and 17]; Friedreich ataxia; and dentate, red nucleus, pallidus, Lewy body atrophy genes) or whole-exome sequencing was also completed if clinically appropriate. Patients were followed up at the clinic or through telephone call on a regular basis.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Ethics Committee of Peking Union Medical College Hospital. All included patients or their deputies provided written informed consent.

Data Availability

Data related to the study are available from the corresponding author and can be shared with any qualified investigator.

Results

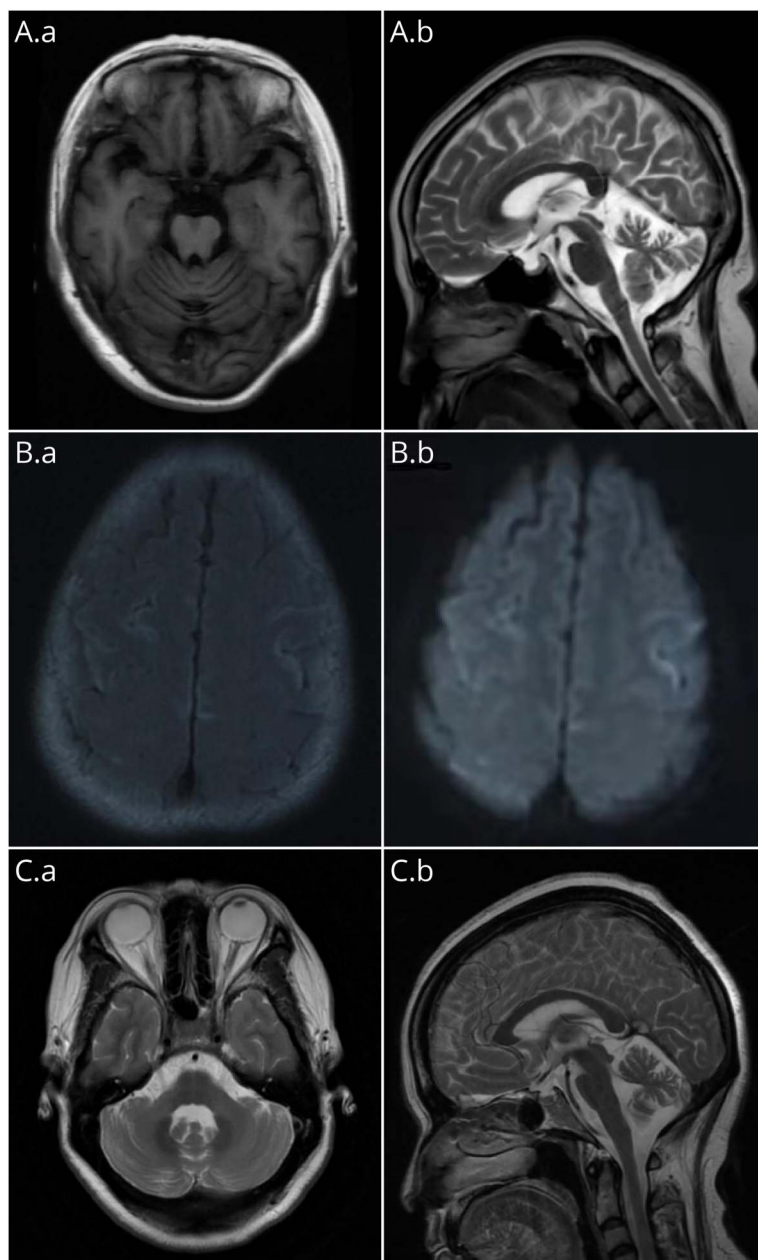
Clinical Presentation

Homer-3 antibodies were identified in 4 female and 2 male patients, one of whom has been previously reported (patient 1).⁷ Although the median age at onset was 54.5 years (range 14–84 years), the autoantibody was also detected in an adolescent (patient 3). Prodromal fever was reported by 1 patient (patient 3). Onset was subacute in 4 and insidious in 2 patients. Their clinical presentation mainly involved the following 3 neurologic syndromes: (1) cerebellar ataxia, (2) encephalopathy and myeloradiculopathy, and (3) RBD and autonomic dysfunction.

Cerebellar involvement was noted in all patients, including dizziness ($n = 6$), unsteady gait ($n = 6$), limb ataxia ($n = 4$), slurred speech ($n = 4$), and nystagmus ($n = 3$). Cerebellar atrophy was identified on brain MRI in 3 patients (Figure 1A).

Patients 3 and 6 exhibited encephalopathy: one patient demonstrated psychosis, seizure, confusion, bilateral frontal and parietal cortex MRI lesions, and epileptiform discharge in EEG and the other patient demonstrated cognitive

Figure 1 Brain MRI Findings in Patients 1, 2, and 6



(A) Cerebellum atrophy (patient 1) (B) fluid-attenuated inversion recovery and diffusion weighted imaging hyperintensity in bilateral frontal and parietal cortex (patient 6), and (C) cerebellum and pons atrophy with hot cross bun sign (patient 2).

impairment and diffuse bilateral cerebral T2 hyperintensity. These 2 patients also showed limb weakness and hyporeflexia. Patient 3's EMG showed abundant spontaneous electrical activity (e.g., fasciculation potential), increased motor unit action potential duration, and reduced recruitment, consistent with denervation, whereas the velocity and amplitude of motor and sensory conductance were within normal limits. Patient 3 also presented with bilateral Babinski sign. Patient 6 was negative for pathologic reflexes, and her EMG was unavailable. Considering their clinical presentations and electrophysiologic examinations, patient 3 was diagnosed with probable myeloradiculopathy and patient 6 with probable radiculoneuropathy.

Of note, 2 patients (patients 2 and 4) showed multiple system atrophy with cerebellar features (MSA-C)-like presentations including dysuria, postural hypotension, and RBD. Their brain MRIs revealed cerebellum and pons atrophy with hot cross bun sign.

Lumbar puncture was completed in all patients. Except for patient 4, whose white blood cell count and protein concentration were influenced by a mixture of blood, leukocytosis and elevated protein were noted in 2 patients and 1 patient, respectively. Oligoclonal bands were identified in 2 of 5 CSF samples.

Chest CT finding revealed pulmonary nodules of potential malignancy in patient 5, but he refused biopsy. Screening for malignancy in other patients was unremarkable. Patient 3 was positive for anti-GM1. Patient 6 had rheumatoid arthritis and Graves disease, which were treated with low-dose prednisone and methimazole, respectively. For all 6 patients, screening for other causes of cerebellar ataxia and encephalitis including metabolism, intoxication and hereditary diseases, and tests for paraneoplastic antibody assays (anti-Hu/Yo/Ri/Ma2/Ta/CV2/amphiphysin antibodies), autoimmune encephalitis antibodies (anti-NMDAR/LGI1/GABA_BR/CASPR2/GAD65/IgLON5/DPPX antibodies), and anti-gluten IgG/IgA were negative.

Identification of Homer-3 Antibody

Examination of the ACA antibody panel (Tr[DNER]/Zic4/ITPR1/Homer-3/NCDN/PKC γ /PCA-2/AP3B2/mGluR1/ATP1A3 antibodies) revealed Homer-3 antibody in the serum of all 6 patients and in the CSF of patient 1 in both cell-based and tissue-based assays (EUROIMMUN, Lübeck, Germany), whereas CSF samples of patients 2–5 were negative. On a fixed monkey cerebellum section, the patients' serum/CSF reacted with the cytoplasm and dendrites of Purkinje cells, whereas the nucleus was spared (Figure 2A), comparable with the existing literature.^{4,7} The antigen was confirmed by a cell-based assay (Figure 2B).

Treatment and Response

All patients received immunotherapy including IV immunoglobulin (IVIg), corticosteroid, plasma exchange, and mycophenolate mofetil, after which most of the patients (n = 4) remained profoundly disabled with modified Rankin Scale score ≥ 3 at the last follow-up (mean follow-up time from symptom onset 44.5 months, range 11–98 months). The residual cerebellar symptoms were significant, as suggested by the Scale for the Assessment and Rating of Ataxia scores, which were available in 3 patients at the last follow-up and ranged from 12 to 29, although 4 patients showed partial improvement and 1 patient showed stabilization regarding ataxia, weakness, and encephalopathy; the remaining patient continued to deteriorate. Moreover, half (n = 2) of the patients who had improved subsequently experienced relapse

during corticosteroid weaning or after they stopped IVIg infusion. In patients 3 and 6, the cerebral lesions on MRI shrank after treatment. At their last follow-up, serum Homer-3 antibody was retested in patients 1, 2, and 3, who all remained positive.

Discussion

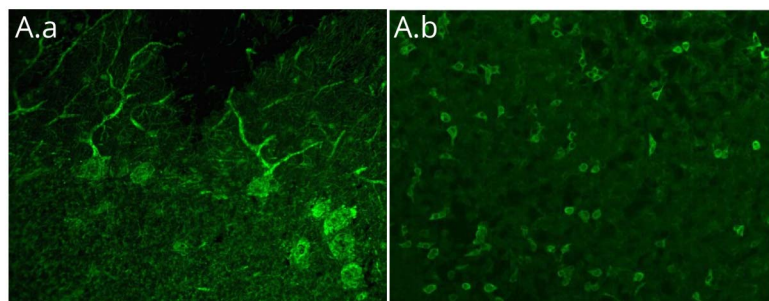
We describe a case series of Homer-3 antibody-associated neurologic disorders from China. Although cerebellar ataxia was the most common manifestation, a wider spectrum of neurologic manifestations was observed, including encephalopathy, radiculoneuropathy/myeloradiculopathy, dysautonomia, and RBD. Immunotherapy could result in a degree of remission, but relapse and severe residual disability were common.

Our findings are comparable with the 2 previously reported patients with Homer-3 antibodies (patients 7 and 8 in Table 1).^{8,9} The previous patients also had acute-onset cerebellar ataxia with or without encephalopathy. Cranial MRI was normal or showed cerebellar atrophy. CSF analyses revealed increased white blood cell count, protein concentration, and IgG index. Immunotherapy resulted in partial improvement or stabilization of their symptoms.

Homer-3 is a postsynaptic scaffolding protein that cross-links mGluR1 (metabotropic glutamate receptor) to ITPR1 (intracellular calcium channel), thereby regulating the calcium equilibrium of Purkinje cells in response to mGluR1 activation.¹⁰ Mutations of mGluR1 and ITPR1 are associated with spinocerebellar ataxia.^{11,12} Cerebellar ataxia is also the most common symptom of anti-mGluR1 autoimmunity.¹³ Homer-3 is enriched in the dendritic spines of Purkinje cells and is expressed in their somata and axons, the cerebellar cortex, hippocampus, and nonneuronal tissues (e.g., thymus and lung).

Although passive transfer experiments have not been performed and the direct effects of Homer-3 antibody on cultured neurons have not been examined, antibodies to other intracellular components (e.g., anti-Yo and anti-Hu) were not

Figure 2 Reactivity of Patients' Serum With Monkey Cerebellum and HEK293 Cells Transfected With Homer-3



(A) Tissue-based assay of patient serum using monkey cerebellum tissue sections showing immunofluorescence of Purkinje cell cytoplasm and dendrites ($\times 200$) and (B) serum Homer-3 antibody detected by cell-based assay (fixed HEK293 cells, $\times 200$).

Table 1 Summary of the Clinical Features of Cases With Homer-3 Antibodies

Patient (sex/age at onset)	Disease duration (mo)	Onset	Neurologic syndrome	MRI (time from onset, mo)	CSF WBC (/μL)/protein (g/L)/OCB	Treatment (outcome)	mRS/SARA score at the last follow-up (mo from onset)
1 (F/46)	60	Insidious	Cerebellar ataxia	Cerebellum atrophy (60)/worsened cerebellum atrophy (98)	0/0.41/+	CS, MMF (partial recovery)	5/29 (98)
2 (F/50)	30	Subacute	Cerebellar ataxia and RBD	Normal (2)/Cerebellum and pons atrophy with hot cross bun sign (16)	2/0.3/-	CS, MMF (partial recovery)	2/12 (31)
3 (M/14)	9	Subacute	Cerebellar ataxia, myeloradiculopathy, and encephalopathy	Diffuse T2 hyperintensity in bilateral cerebral hemispheres (1)/decrease of T2 hyperintensity (8)	21/0.61/+	Partially improved after IVIg and CS but relapsed twice during weaning from CS	3/19 (40)
4 (M/65)	24	Insidious	Cerebellar ataxia and RBD	Cerebellum and pons atrophy (13)/cerebellum and pons and cerebellum peduncle atrophy with hot cross bun sign (24)	30/1.136/ ^a	IVIg, CS, PLEX (deteriorated)	4/NA (64)
5 (F/84)	3	Subacute	Cerebellar ataxia	Normal (3)/normal (9)	6/0.48/NA	CS (stable)	2/NA (23)
6 (F/59)	9	Subacute	Cerebellar ataxia, radiculoneuropathy, and encephalopathy	FLAIR hyperintensity in bilateral cerebral cortex (9)/normal (10, after IVIg treatment)	2/0.17/-	IVIg (improvement followed by relapse) and CS (improvement)	4/NA (11)
7 (F/65)	1	Acute	Cerebellar ataxia	Normal (1)	27 lym/NA/increased IgG index	CS (stable)	NA
8 (M/38)	NA	Acute	Cerebellar ataxia and encephalopathy	Normal/cerebellar atrophy (10 mo after diagnosis)	60/1.11/-	IVIg and CS (partial improvement)	2/NA (24)

Abbreviations: CS = corticosteroid; FLAIR = fluid-attenuated inversion recovery; IVIg = IV immunoglobulin; MMF = mycophenolate mofetil; mRS = modified Rankin Scale; NA = not available; OCB = oligoclonal bands; PLEX = plasma exchange; SARA = Scale for the Assessment and Rating of Ataxia.
^a Results affected by traumatic lumbar puncture.

pathogenic in animal experiments,^{14,15} indicating that pathogenicity of Homer-3 antibody itself is unlikely and the pathogenicity might be mediated by T lymphocytes.^{2,4}

Notably, 2 patients in our cohort had clinical presentations and imaging findings very similar to patients with MSA-C. RBD, hot cross bun sign, and dysautonomia observed in these patients are considered diagnostic markers for MSA-C¹⁶; however, all have been reported in autoimmune, paraneoplastic, and hereditary CNS diseases, and some respond to immunotherapy.¹⁷⁻²⁴ Homer-3 antibody might also be related to dysfunction of the autonomic and sleep-regulating neurology networks and atrophy of cerebellar afferent and efferent fibers.

As reported in previous studies of anti-Homer-3-associated ataxia,^{8,9} screening for this antibody in hundreds of healthy controls and patients with other types of cerebellar ataxia was negative, suggesting that Homer-3 antibody has high specificity. Given that MSA-C is a progressively deteriorating degenerative disease lacking effective treatment, whereas Homer-3 antibody-associated cerebellar syndrome can respond to immunotherapy, recognition of a potential autoimmune etiology among MSA-C-like patients is important. However, Homer-3 antibody-associated cerebellar ataxia is much rarer than MSA-C, making unbiased screening

for the antibody clinically impractical. According to this study, acute or subacute onset, cerebral and nerve root involvement, lack of dysautonomia, and inflammatory changes in CSF may serve as clues. In the future, more features may be identified to aid in the differentiation between autoimmune MSA-C mimics and degenerative MSA-C.

Patient 3 was weakly positive for anti-GM1 in serum, which may be a bystander of the disease course or may coexist with anti-Homer 3, such that both antibodies contribute to the autoimmune pathogenicity and radiculopathy/peripheral neuropathy in this patient. Given the wide clinical spectrum related to the presence of Homer-3 antibody, other unidentified concomitant autoantibodies may be responsible for some of the patients' neurologic findings.

Four of the 6 patients in our cohort could not live independently at the last follow-up, although some partially improved or stabilized after immunotherapy. The unfavorable outcome might be explained by the delayed treatment, as suggested by the presence of existing cerebellar atrophy. Moreover, even in patients with cerebellar ataxia related to cell surface antibodies (e.g., anti-mGluR1, antiseizure-related 6 homolog-like 2, and anti-NMDAR), the outcome is usually worse than the results in patients with autoimmune encephalitis,^{13,25} which suggests that the cerebellum is

vulnerable to immune damage and secondary degeneration of cerebellar circuits. Timely, comprehensive, and even aggressive immunotherapy may be warranted for patients with Homer-3 antibody-associated diseases to avoid severe disability.

In conclusion, anti-Homer 3-related cerebellar ataxia can mimic MSA-C in both clinical and neuroimaging characteristics. A lack of profound autonomic dysfunction, cerebral involvement, or subacute onset should raise a suspicion of an etiology other than degeneration. Timely diagnosis is important because immunotherapy may prevent further neuronal loss and clinical deterioration.

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Disclosure

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Appendix (continued)

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