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Short Communication

Anti-Homer-3 antibody associated cerebellar ataxia: A rare case report and literature review

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ABSTRACT

Anti-Homer-3 antibody associated cerebellar ataxia is a rare autoimmune cerebellar ataxia, which had been previously reported in 2 cases only. Here we present the third case where a middle-aged female experienced progressive cerebellar ataxia. A novel cerebellar ataxia antibody panel indicated sera of the patient was positive for anti-Homer-3 antibodies and established the diagnosis. Given steroids and long-term mycophenolate mofetil, the patient experienced partial improvement and remained stable in the follow-ups. Our report indicated immune-mediated causes should be considered in the context of 'idiopathic' cerebellar ataxia and immunotherapy could have therapeutic effects.

1. Case report

A 51-year-old female was admitted in Aug 2017 because of dizziness, slurred speech, unsteady gait for 5 years and numbness for 6 months.

The patient first experienced occasional dizziness in 2012 and gradually developed double vision, tremor and slurred speech. Her symptoms progressed with newly developed unsteady gait in 2015, disabling her from standing and performing fine hand movements. In Feb 2017, she started to experience numbness in her extremities. She lost 25 kg of weight in five years.

Her past medical history was remarkable for hypertension and type 2 diabetes mellitus (T2DM), both were well controlled. Her family history was unremarkable.

Previous brain magnetic resonance imaging (MRI) in 2013 revealed cerebellum atrophy, while various infectious, metabolic, genetic, vascular and other tests at local hospitals were negative (Supplement Table 1). The patient was considered of idiopathic cerebellar ataxia and referred to our hospital.

In clinic, the patient was awake and alert but unable to stand. Neurological examinations demonstrated dysarthria and bilateral horizontal nystagmus. Tremor and dysmetria were noted. Examination of lower extremities revealed decreased distal muscle strength (dorsiflexion 3/5, plantaflexion 4/5) and disappeared reflexes. Her sensory system was intact.

Complete blood count (CBC), biochemical tests, serum screening tests of infection, toxin, metabolic and systemic autoimmune diseases were unremarkable. Serum tumor markers, paraneoplastic antibody assays (anti-Hu/Yo/Ri/Ma2/Ta/CV2/amphiphysin antibody), autoimmune encephalitis antibodies (anti-NMDAR/LGI1/GABAb/CASPR2/DPPX antibody) and antibodies against AQP-4, GM1 were negative. EMG was insignificant.

Lumbar puncture revealed opening pressure of 155mmH_2O with normal biochemical tests and cytology. Cerebral spinal fluid (CSF) screening of infection and paraneoplastic antibodies were negative. However, oligoclonal band (OCB) was positive with IgG index of 0.49.

Repeated MRI indicated atrophy of cerebellum hemispheres (Fig. 1 A-D). Her positron emission tomography-computed tomography (PET-CT) was unremarkable. Autoimmune cerebellar ataxia (ACA) panel was performed with both cell-based and tissue-based assay (Euroimmun, Lübeck, Germany), including anti-Neurochondrin (NCDN) antibody, anti-Tr, delta notch-like epidermal growth factor-related receptor (DNER) antibody, anti-Purkinje cell antibody 2 (PCA2) antibody, anti-Homer protein homolog 3 (Homer-3) antibody, anti-glutamate decarboxylase 65 (GAD65) antibody, anti-ZIC4 antibody, anti-inositol 1, 4,5-trisphosphate receptor 1 (ITPR1) antibody and anti-carbonic anhydrase-related protein (CARP) antibody.

The patient was positive for serum anti-Homer-3 antibody with the titer of 1:320 (Fig. 2 A-B), which was repeated and confirmed by Euroimmun laboratory in Germany. Diagnosis of anti-Homer-3

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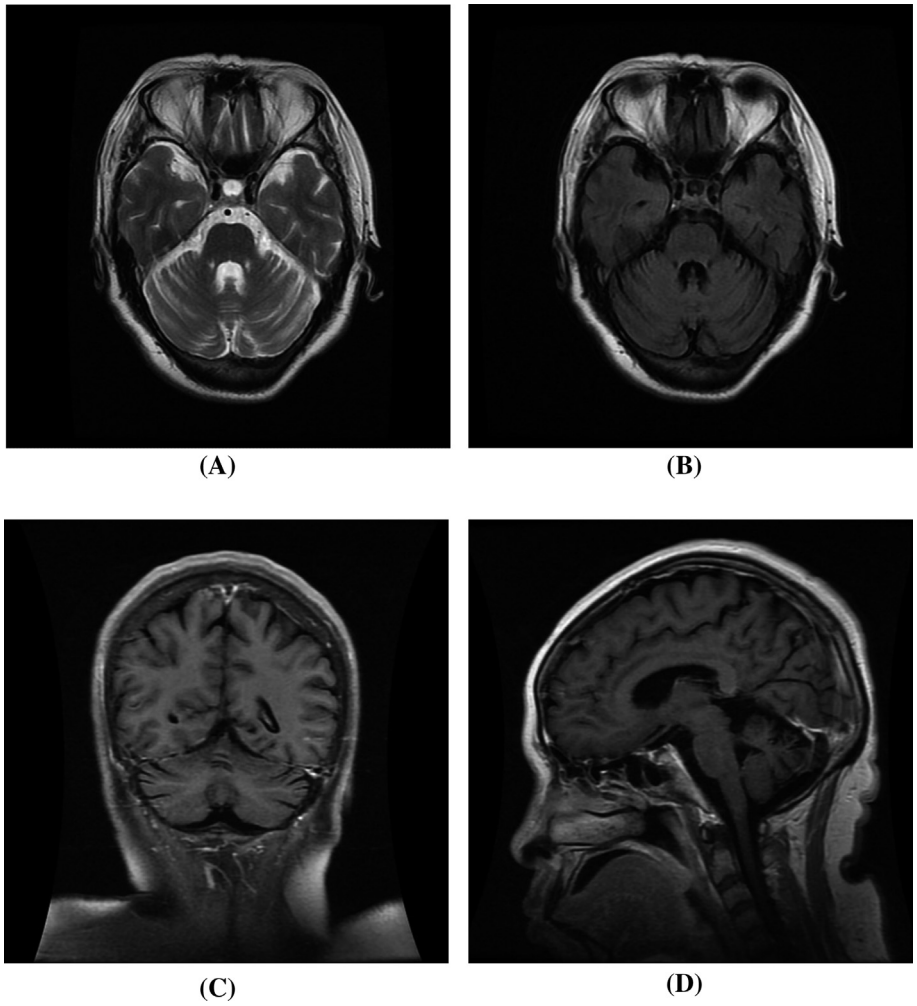

Fig. 1. (A–D): Brain MRI of the patient indicated bilateral cerebellar hemisphere atrophy. (A, B) Widening of cerebellar fissure on cross section view of cerebellum on T2 and FLAIR sequence. (C, D) Atrophy of cerebellum with no enhancement on horizontal and sagittal view. Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid attenuated inversion recovery.

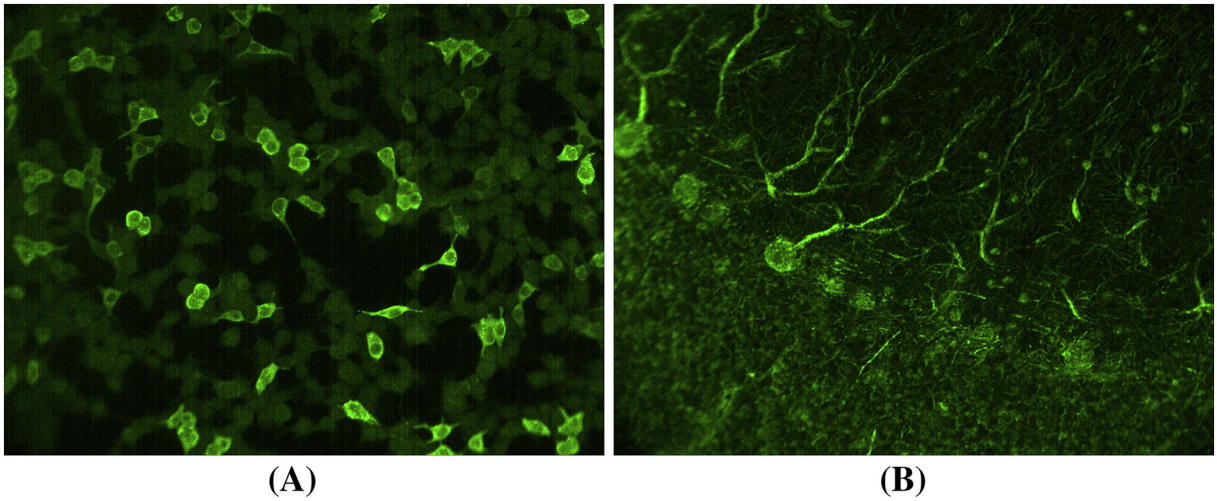

Fig. 2. (A-B): Immunofluorescence of the Patient's serum. (A) Antibody from the patient's serum recognizes Homer-3 antigens in fixed HEK293 cells. (B) Binding of serum anti-Homer-3 antibody from the patient to monkey cerebellum tissue sections.

antibody associated cerebellar ataxia was made and she was given intravenous methylprednisolone 1000 mg for 3 days, followed by 500 mg for 3 days, 250 mg for 3 days and taped to oral prednisone 60 mg/day. Her dizziness and dysmetria improved and she was discharged in Sep 2017.

The patient gradually transferred to steroid-sparing agent mycophenolate mofetil (MMF) 1.5 g/d and was regularly monitored on modified Ranking scale (mRs), CD19(+) B cell count (Supplement

Table 1
Summary of the clinical features of cerebellar ataxia with anti-Homer-3 antibodies.

No./Study	Age/Gender	Onset	Symptoms	Tumor	MRI at onset/Follow-up (mo)	CSF WBC (/ul)/protein level (g/l)/IgG index	Treatment	Outcome (Follow-up,mo)
1. Zuliani et al., 2007	65/F	Subacute	Vertigo, vomiting, dysarthria,limb and gait ataxia	No	normal/NA	27/normal/1.4	Steroids	No improvement (72)
2. Hoftberger et al., 2013	38/M	Acute	Nausea, vomiting, pancerebellar syndrome, complex partial seizures	No	Normal/mild atrophy of the vermis and cerebellar hemispheres (10)	60/1.11/normal	IVIG, steroids	Partial recovery (24)
3. Current study	51/F	Insidious	Dizziness, slurred speech, unsteady gait	No	Cerebellum atrophy/cerebellum atrophy (48)	0/0.41/0.49	Steroids, MMF	Partial recovery (12)

Table 2 and Fig. 1) and anti-Homer-3 antibody. At last visit in Aug 2018, she was able to stand on her own for 15 min with improved dizziness and slurred speech. Her mRs decreased from 4 to 3, antibody titer dropped to 1:100 and CD19(+) B cell count descended from 720/ul to 367/ul (reference level 160–350/ul).

2. Discussion

We described a rare case of anti-Homer-3 antibodies associated cerebellar ataxia. Previous two cases were identified in a 65-year-old female (Zuliani et al., 2007) and a 38-year-old male (Hoftberger et al., 2013) with acute or subacute onset and treated with steroids/IVIG. Clinical features of these patients were summarized in Table 1.

Cerebellum ataxia may be caused by infectious, metabolic, genetic and immune diseases. In 'idiopathic' later-onset cerebellar ataxia, the underlying pathogenic mechanism is still to be elucidated. However, some of these patients have been proved to suffer from immunologically mediated diseases actually (Burk et al., 2001; Hadjivassiliou et al., 1998; Meinck et al., 2001; Selim and Drachman, 2001) and autoimmunity can be a prognostic factor (Sivera et al., 2012).

Our patient experienced onset of cerebellar symptoms in her 50s and extensive screening of infectious, metabolic, vascular, hereditary causes was unrevealing. She was previously diagnosed with 'idiopathic' cerebellar ataxia and delayed treatment may contribute to the slow progression of her symptoms.

OCB of the patient's CSF strongly indicated immune-mediated pathogenesis, which can be classified as paraneoplastic and non-paraneoplastic. Thorough tumor screening and paraneoplastic assays ruled out paraneoplasctic causes. Screening for systemic autoimmune antibodies was unremarkable. However, AC autoantibodies screening was positive and detection of well-characterized anti-Purkinje cell autoantibodies established a concrete diagnosis.

Homer-3 predominantly expresses on Purkinje cell dendrites spines (Shiraishi et al., 2004) and is the scaffold protein interacting with mGluR1 and inositol 1,4,5 triphosphate receptors (IP3R), regulating calcium metabolism (Beqollari and Kammermeier, 2013). Although the pathogenic role of anti-Homer-3 antibody is yet to be clarified, the antibody indicated underlying autoimmune process thus timely diagnosis and immunotherapy could be beneficial. A cohort study of 118 ACA patients (Meinck et al., 2001) found improvement was more common in nonparaneoplastic patients and slow tapering of immunotherapy up to 6 months was more effective than short courses ranging from days to weeks. In our case, the partial response in our patient may due to delayed diagnosis and loss of Purkinje cells at initial course, as in Zuliani, L's report (Zuliani et al., 2007). Nevertheless, long-term MMF combined with steroids helped to halt and minimize cerebellar ataxia.

However, evaluation of these patients remains challenging because of the slow progressive clinical characters and the relative coarse nature of mRs. The rarity of the disease also limited interpretation of outcome.

In summary, we report a rare ACA case with anti-Homer-3 antibody and improved partially on long-term immunotherapy. Although diagnosing cerebellar ataxia remains challenging, autoimmune causes should be taken into consideration because of potential treatment efficacy.

Declarations of interest

None.

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Appendix A. Contribution of the authors

Name	Location	Role	Contribution
Xiaolu Xu,-MD	Department of Neurology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China	Author	Design and conceptualized study; drafted the manuscript for intellectual content
Haitao Ren	Department of Neurology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China	Author	Performed and interpreted the antibody testing results
Libo Li,MD	Department of Neurology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China	Author	Acquisition of clinical information and data
Jing Wang, phD	CAS Key Laboratory of Mental Health, Institute of Psychology, Department of Psychology, Chinese Academy of Sciences, Beijing, China	Author	Design and conceptualized study; revised the manuscript for intellectual content
Fechner Kai, phD	Institute of Experimental Immunology, affiliated to Euroimmun AG, Lübeck, Germany	Author	Performed and interpreted the antibody testing results
Hongzhi Guan, MD	Department of Neurology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China	Author	Design and conceptualized study; interpreted the results; revised the manuscript for intellectual content

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2019.01.002.

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