Case report and literature analysis: Autoimmune cerebellar ataxia associated with homer-3 antibodies

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Objective: We present a case of autoimmune cerebellar ataxia (ACA) associated with Homer protein homolog 3 (Homer-3) antibodies. Then, a review of the literature was conducted to summarize its clinical spectrum to improve clinicians’ understanding of this rare entity.

Case presentation: A 25-year-old man suffered from the subacute onset of cerebellar ataxia and psychiatric symptoms with abnormalities in the cerebellum on initial brain MRI and Homer-3 antibodies titers of 1:100 in the serum. His neurological symptoms did not improve after intravenous methylprednisolone but significantly improved following plasma exchange with a modified Rankin Scale (mRS) score of 1. However, 5 months later, he experienced relapse during oral prednisone tapering with enhanced cerebellar lesions and obvious cerebellar atrophy on repeated MRI. Various immunomodulatory approaches, including corticosteroids and plasma exchange, were utilized with no improvement. Then rituximab was given for the first time to treat Homer-3 autoimmunity with partial improvement of symptoms. However, the patient remained profoundly disabled with an mRS score of 4.

Conclusion: ACA associated with Homer-3 antibodies may have a suboptimal response to corticosteroid therapy. More intense immunotherapy such as rituximab may contribute to the improvement of cerebellar syndrome. Relapsing courses and presentation of cerebellar atrophy may suggest a poor prognosis in this entity.

KEYWORDS
autoimmune cerebellar ataxia, Homer-3 antibody, brain MRI enhanced abnormalities, relapse, rituximab

Introduction

Autoimmune cerebellar ataxia (ACA) associated with Homer protein homolog 3 (Homer-3) antibodies is a rare disease. To the best of our knowledge, only 11 cases have been reported in the literature (1–6). The whole clinical spectrum and potential treatment options remain obscure. Here, we present a well-characterized case of
Homer-3 autoimmunity, a 25-year-old man who experienced clinical relapse with enhanced abnormalities in the cerebellum on brain magnetic resonance imaging (MRI) that has not been reported in previous studies, and in whom rituximab was initiated for the first time with partial improvement of symptoms. Then, we reviewed and analyzed all ACA cases associated with Homer-3 antibodies, summarizing the clinical presentations, diagnostic considerations, imaging findings, treatment, and prognosis of this disease. Our purpose was to aid in the clinical understanding of this rare entity.

Case presentation

A 25-year-old man was admitted because of the subacute onset of vertigo, nausea, and vomiting for 2 weeks with slurred speech and unsteady gait for 1 week. He denied symptoms of previous infectious diseases. His past medical and family history was unremarkable. In the clinic, the patient was alert but unable to walk without help. Neurological examination demonstrated dysarthria, bilateral horizontal nystagmus, moderate limb dysmetria, and gait ataxia with a scale for the assessment and rating of ataxia (SARA) score of 20. The modified Rankin Scale (mRS) score on admission was 4. Initial brain MRI was performed and showed hyperintensities in the vermis and bilateral cerebellar hemispheres on fluid-attenuated inversion recovery (FLAIR) without enhancement (Figures 1A–F). Cerebrospinal fluid (CSF) study revealed an elevated opening pressure of 200 mmH2O, mild pleocytosis (white blood cell count 50/ul, 88% lymphocytes; reference range: 0–8/ul), elevated protein level (0.63 g/L; reference range: 0.1–0.45 g/L) and increased CSF IgG index (74.7 mg/L; reference
Patients’ age ranged from 10 to 40 years (mean ± SD: 23.01 ± 43.92), seven (58.33%) were women. Then, two patients had a history of prodromal infection. The onset was subacute/acute in nine and insidious in three. Serum and CSF paraneoplastic antibodies (anti-Hu, anti-Yo, anti-Ri, amphiphysin, and other antibodies, and non-paraneoplastic antibodies including GAD65, AP3B2, neurochondrin, septin-5 and Homer-3 antibodies) were either negative or in the normal range. Remarkably, repeated cerebral MRI indicated obvious cerebellar atrophy and worsened cerebellar lesions with gadolinium enhancement. Repeat screening for neoplasia has been negative.

Clinical presentations

A total of twelve cases, including ours, have been described in this study (Table 1) (1–6). Patients’ age ranged from 10 to 84 years (mean ± SD: 43.92 ± 23.01), seven (58.33%) were women. Then, two patients had a history of prodromal infection. The onset was subacute/acute in nine and insidious in
three patients. Cerebellar symptoms were noted in all patients, including vertigo, nausea, vomiting, nystagmus, head intention tremor, speech dysarthria, limb dysmetria, and gait ataxia. A total of five patients exhibited symptoms of encephalopathy including psychosis \((n = 3)\), seizures \((n = 2)\), confusion \((n = 1)\) and cognitive impairment \((n = 2)\). Other extracerebellar features included myeloradiculopathy \((n = 2)\), REM sleep behavior disorder \((n = 2)\) and autonomic dysfunction \((n = 2)\). Except for one patient with pulmonary nodules of potential malignancy, extensive studies failed to reveal any tumor in these patients.

### Diagnostic investigations

The detailed CSF data were available for all 12 patients with inflammatory changes: lymphocytic pleocytosis was noted in seven patients \((\text{cell counts} \, 21–139/\mu l)\), elevated protein was noted in four patients \((0.61–1.67 \, g/l)\), and intrathecal IgG synthesis was elevated in six patients. Besides, Homer-3 antibodies were detected in CSF of three patients \((\text{the CSF antibody panel was not performed in case 2, case 3, and case 4})\) and in serum of 11 patients, which indicated that serum and CSF testing is mandatory when ACA is considered. Ideally, both cell-based and tissue-based assays should be used to test for Homer-3 antibodies. However, we did not conduct a tissue-based assay, which was a limitation of this report.

Initial brain MRI was performed in all patients with variable manifestations, which were normal \((n = 4)\), and showed bilateral cerebral/cerebellar abnormalities \((n = 5)\) or cerebellar atrophy \((n = 3)\). Repeated MRI was obtained in 10 patients on follow-up at 1.5–98 months. The cerebral/cerebellar lesions were reported to shrink after treatment in three patients. Nevertheless, the follow-up MRI in our patient showed enhanced cerebellar lesions which have not been reported in previous studies, indicating evidence of cerebellar inflammation. Moreover, it is important to note that in more than half of the patients \((6 \, \text{out of} \, 10)\), the repeated MRI disclosed cerebellar or pontine atrophy after comprehensive immunotherapy, which is probably the result of the secondary degeneration of cerebellar circuits after cerebellar inflammation \((4, 13, 14)\).

### Treatment and prognosis

There are no standards for the treatment of Homer-3 autoimmunity. First-line immunotherapies in the acute phase including corticosteroids, intravenous immunoglobulins \((IVIg)\), and plasma exchange may be beneficial \((1–6)\). Besides, long-term immunosuppression such as oral prednisone and mycophenolate mofetil \((MMF)\) was administered in some patients for the possibility of long-term clinical benefit, which was reported to halt and minimize cerebellar ataxia in Homer-3 autoimmunity \((2–5)\). However, the response to immunotherapy was equivocal. In our patient, treatment with methylprednisolone did not improve the symptoms in the acute phase and maintenance therapy of oral prednisone did not prevent the occurrence of clinical relapse and cerebellar atrophy. In this situation, intravenous rituximab was given for the first time to treat Homer-3 autoimmunity, and partial
TABLE 1  Review all reported ACA cases with Homer-3 antibodies.

| Case | Age/Gender | Onset | Neurological symptoms | Tumor | Initial/Follow-up MRI (months from onset) | Detection of Homer-3 antibodies | CSF WBC (/µl)/protein(g/l)/intrathecal IgG synthesis | Treatment | Outcome/mRS (months from onset) |
|------|------------|-------|-----------------------|-------|------------------------------------------|---------------------------------|---------------------------------|-----------|-----------------------------|
| 1    | 25/M       | Subacute | Cerebellar syndrome and psychiatric symptoms | No    | FLAIR hyperintensities in cerebellar hemispheres and vermis/worsened cerebellar lesions with enhancement and obvious cerebellar atrophy (5) | Serum 50/0.63/increased IgG index | CS, PLEX, rituximab | Partially improved but relapsed/4(11) |
| 2    | 65/F       | Subacute | Cerebellar syndrome | No    | Normal/NA | Serum* 27/NA/increased IgG index | CS | No improvement/NA(68) |
| 3    | 38/M       | Acute | Cerebellar syndrome and complex partial seizures | No    | Normal/mild cerebellar atrophy (10) | Serum* 60/1.11/no IVIg, CS | Partially improved/2(24) |
| 4    | 51/F       | Insidious | Cerebellar syndrome | No    | Cerebellar atrophy/cerebellar atrophy (48) | Serum* 0/0.41/OCB positive | CS, MMF | Partially improved/3(12) |
| 5    | 46/F       | Insidious | Cerebellar syndrome | No    | Cerebellar atrophy/worsened cerebellar atrophy (98) | Serum and CSF 0/0.41/OCB positive | CS, MMF | Partially improved/5(98) |
| 6    | 50/F       | Subacute | Cerebellar syndrome and RBD | No    | Normal/Cerebellar and pontine atrophy (16) | Serum 2/0.3/no | CS, MMF | Partially improved/2(31) |
| 7    | 14/M       | Subacute | Cerebellar syndrome, cognitive impairment and myeloradiculopathy | No    | Diffuse T2 hyperintensity in bilateral cerebral hemispheres/decrease of T2 hyperintensity (8) | Serum 21/0.61/OCB positive | IVIg, CS | Partially improved but relapsed twice/3(40) |
| 8    | 65/M       | Insidious | Cerebellar syndrome and RBD | No    | Cerebellar and pontine atrophy/worsened cerebellar and pontine atrophy (24) | Serum 30/1.136/NA | IVIg, CS, PLEX | Deteriorated/4(64) |
| 9    | 84/F       | Subacute | Cerebellar syndrome | Potential malignant pulmonary nodules | Normal/normal (9) | Serum 6/0.48/NA | CS | No improvement/2(23) |

(Continued)
TABLE 1 Continued

| Case | Age/Gender | Onset | Neurological symptoms | Tumor | Initial/Follow-up MRI (months from onset) | Detection of Homer-3 antibodies | CSF WBC (x10⁶) | Protein (g/l) | Intrathecal IgG synthesis | Treatment | Outcome/mRS (months from onset) |
|------|------------|-------|-----------------------|-------|------------------------------------------|-------------------------------|----------------|--------------|----------------------------|-----------|-------------------------------|
| Case 10 | 59/F | Subacute | Cerebellar syndrome, psychosis, seizure, confusion and radiculoneuropathy | No | FLAIR hyperintensity in bilateral cerebral cortex (normal) | Serum | 2/0.17/no | FLAIR positive | Negative | IVlg, CS | Improved followed by relapse (411) |
| Case 11 | 20/F | Subacute | No | T2 FLAIR hyperintensity in the right cerebellar hemisphere/normals (1.5) | Serum and CSF | 2/0.16/OCB | Positive | IVlg, CS | MMF | Obviously improved (38) |
| Case 12 | 10/M | Subacute | Cerebellar syndrome, cognitive impairment and irritability | NA | T2 and FLAIR hyperintensity in cerebellar hemispheres and vermis/NA | CSF | 30/0.3/NA | MMF | IVlg, CS | Improved (11) |

*The antibody panel was not performed in CSF.

ACAS, autoimmune cerebellar ataxia; CS, corticosteroid; FLAIR, fluid attenuated inversion recovery; IVlg, IV immunoglobulin; MRI, magnetic resonance imaging; OCB, oligoclonal bands; PLEX, plasma exchange; WBC, white blood cell.

improvement was observed. This may indicate that more intense immunotherapy such as rituximab could be a second choice when the first-line treatment did not work out.

The overall outcome of this disease was poor. Only 4 patients were reported to achieve a good functional outcome (mRS ≤2) and almost all the patients ended up with neurological sequelae. This is partially explained by cerebellar atrophy, a possible complication of ACA associated with Homer-3 antibodies (1–6, 14). Moreover, it is important to highlight that three patients including our patient experienced clinical relapse during corticosteroid tapering or weaning or after they stopped IVlg infusion (4). The fact that these patients remained profoundly disabled may imply that relapsing courses can lead to a poor prognosis.

**Conclusion**

In patients with Homer-3 autoimmunity, extensive studies failed to reveal any tumor, MRI findings were variable, CSF always presented with inflammatory changes, Homer-3 antibodies were detected in serum or CSF and the response to immunotherapy treatment was equivocal. Intravenous rituximab may partially improve cerebellar symptoms, especially in relapsing cases. The neurologic prognosis depends on multiple factors. Relapsing courses and presentation of cerebellar atrophy may suggest that recovery will be incomplete.

**Data availability statement**

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

**Ethics statement**

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

**Author contributions**

QW made substantial contributions to study concept and design, interpretation of clinical data, drafting of the manuscript, and fund obtaining. BG made contributions to the acquisition, analysis, and interpretation of imaging data. AJ conducted the literature review and drafted the manuscript. QW and XQ were
involved in revising the manuscript critically and have given final approval for the version to be published. All authors read and approved the manuscript.

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References

1. Zuliani L, Sabater L, Saiz A, Baiges JJ, Giometto B, Graus F. Homer 3 autoimmunity in subacute idiopathic cerebellar ataxia. Neurology. (2007) 68:239–40. doi: 10.1212/01.wnl.0000251308.79366.9
2. Höfberger R, Sabater L, Ortega A, Dalmau J, Graus F. Patient with homo3 antibodies and cerebellitis. JAMA Neurol. (2013) 70:506–9. doi: 10.1001/jamaneurol.2013.1955
3. Xu X, Ren H, Li L, Wang J, Fechner K, Guan H. Anti-Homer-3 antibody associated cerebellar ataxia: a rare case report and literature review. J Neuroimmunol. (2019) 330:155–58. doi: 10.1016/j.jneuroim.2019.01.002
4. Liu M, Ren H, Fan S, Zhang W, Xu Y, Zhao W, et al. Neurological autoimmunity associated with Homer-3 antibody: a case series from China. Neurol Neuroimmunol Neuroinflamm. (2021) 8:e1077. doi: 10.1212/NXI.0000000000010177
5. Miao A, Yu C, Sun Y, Wang L, Ge J, Wang X. Acute Cerebellitis associated with anti-Homer 3 antibodies: a rare case report and literature review. Front Neurol. (2022) 13:837937. doi: 10.3389/fneur.2022.837937
6. Kuang Z, Barazabal-Carvallo J, Mofatteh M, Xie S, Wang Z, Chen Y. Anti-Homer-3 antibody encephalitis in a 10-year-old child: case report and review of the literature. Front Neurol. (2022) 13:929778. doi: 10.3389/fneur.2022.929778
7. Emeloffwonu JA, Shetty J, Kalaperumal C, Gallo P, Sokol D, et al. Acute cerebellitis in children: a variable clinical entity. J Child Neurol. (2018) 33:675–84. doi: 10.1177/0883073818777673
8. Narayan RN, McKeon A, Fife TD. Autoimmune vestibulocerebellar syndromes. Semin Neurol. (2020) 40:97–115. doi: 10.1055/s-0039-3402061
9. Jarius S, Wildemann B. ‘Medusa-head ataxia’: the expanding spectrum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part I: Anti-mGluR1, anti-Homer-3, anti-Sj/iTPPR1 and anti-CARP VIII. J Neuroinflammation. (2015) 12:166. doi: 10.1186/s12974-015-0356-y
10. Jarius S, Wildemann B. Medusa head ataxia: the expanding spectrum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part 2: Anti-PKC-gamma, anti-GluR-delata2, anti-Ca /ARHGAP26 and anti-VGCC. J Neuroinflammation. (2015) 12:167. doi: 10.1186/s12974-015-0357-x
11. Jarius S, Wildemann B. Medusa head ataxia: the expanding spectrum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part 3: Anti-Yo/CDR2, anti-Nb/AP3B2, PCA-2, anti-Tr/DNER, other antibodies, diagnostic pitfalls, summary and outlook. J Neuroinflammation. (2015) 12:168. doi: 10.1186/s12974-015-0358-9
12. Mizutani A, Kuroda Y, Futatsugi A, Furuchi T, Mikoshiba K. Phosphorylation of Homer3 by calcium/calmodulin-dependent kinase II regulates a coupling state of its target molecules in Purkinje cells. J Neurosci. (2008) 28:5369–82. doi: 10.1523/JNEUROSCI.4738-07.2008
13. Spatola M, Petit Pedrol M, Maudes E, Simabukuro M, Muñiz-Castrillo S, Pinto AL, et al. Clinical features, prognostic factors, and antibody effects in anti-mGluR1 encephalitis. Neurology. (2020) 95:e3012–25. doi: 10.1212/WNL.0000000000010854
14. Mulroy E, Balint B, Bhatia KP. Homer-3 antibody disease: a potentially treatable MSA-C mimic. Mov Disord Clin Pract. (2022) 9:178–82. doi: 10.1002/mdc3.13404

Conflict of interest

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