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ORIGINAL ARTICLE

Autoimmune Cerebellar Ataxia: Etiology and Clinical Characteristics of a Case Series from China

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Abstract

Autoimmune cerebellar ataxia (ACA) is an important and potentially treatable cause of sporadic cerebellar syndrome, but studies with large sample size are limited. This study reported a large ACA series in China and described its etiology and clinical characteristics. We reviewed all ACA patients from our hospital (2013–2021) and analyzed their clinical and paraclinical features, treatment, and outcome. ACA subtypes investigated included paraneoplastic cerebellar degeneration (PCD), primary autoimmune cerebellar ataxia (PACA), anti-glutamate decarboxylase (GAD)–associated cerebellar ataxia, opsoclonus-myoclonus syndrome (OMS), Miller Fisher syndrome (MFS), and ACA-associated with autoimmune encephalitis. A total of 127 patients were identified and 40.9% were male. The median onset age was 47.0 years. Gait ataxia was the most prevalent feature followed by limb ataxia, dizziness, and dysarthria/dysphagia. Extracerebellar manifestations included pyramidal signs (28.3%) and peripheral neuropathy/radiculopathy (15.0%). ACA subtypes were PCD (30.7%), PACA (37.8%), ACA associated with autoimmune encephalitis (12.6%), anti-GAD-associated ACA (8.7%), MFS (7.1%), and OMS (3.1%). Neuronal antibodies were positive in 67.7% of patients. Brain magnetic resonance imaging was unremarkable (55.7%) or showed atrophy (18.3%) or abnormal signal intensity (26.1%, most of which was extracerebellar). Although most patients received immunotherapy, the modified Rankin scale at last follow-up was ≤ 2 in only 47.3% patients. Thirteen patients died and 24 relapsed. Compared with PACA, PCD patients were older and had poorer outcome. This study illustrates the heterogeneity in the clinical features of ACA and suggests the importance of neuronal antibody testing in ACA diagnosis. PCD and PACA are the dominant ACA subtypes, and the former has a less favorable prognosis.

Keywords Autoimmune cerebellar ataxia · Paraneoplastic cerebellar degeneration · Primary autoimmune cerebellar ataxia · Prognosis

Introduction

Autoimmune cerebellar ataxia (ACA) contributes to a considerable proportion of sporadic cerebellar syndrome cases [1]. The subtypes of ACA include paraneoplastic cerebellar degeneration (PCD), glutamate decarboxylase (GAD) antibody-related cerebellar ataxia, opsoclonus-myoclonus syndrome (OMS), Miller Fisher syndrome (MFS), and gluten ataxia (GA), according to specific clinical manifestations, speculated triggers, or related autoantibodies [2].

To date, approximately 30 cerebellum autoantibodies have been discovered, and novel ones are consistently being identified [3]. These antibodies serve as pivotal markers for autoimmune etiology in patients with cerebellar ataxia. Some of these antibodies can support the diagnosis of primary autoimmune cerebellar ataxia (PACA) [4].

However, as a rare and heterogeneous disease, literature on ACA is usually case reports of small case series. This study reported an ACA case series with 127 patients from a tertiary neurology referral center from China, analyzing their clinical presentation, neuronal antibody and etiology distribution, and prognosis.

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Materials and Methods

Patients

From March 2013 to October 2021, patients in Neurology Department of Peking Union Medical College Hospital (Beijing, China) were included in this study if they had cerebellar syndrome as the main manifestation and met the diagnostic criteria of PCD, PACA, or glutamic acid decarboxylase (GAD) antibody-related cerebellar ataxia [5]. Patients with other neuroimmune diseases including OMS, MFS, and autoimmune encephalitis were included if cerebellar ataxia was the predominant or one of the major symptoms. Subjects with sensory ataxia and central nervous system inflammatory demyelinating diseases were excluded. The diagnostic criteria of PCD were: conform to the "definite or probable paraneoplastic neurological syndrome (PNS)" in the 2021 edition of the diagnostic criteria [6]. The diagnostic criteria of PACA (Table 1) are modified according to those proposed by Hadjivassiliou et al. [4]. We included patients with cerebellum autoantibodies regardless of the cerebrospinal fluid (CSF) findings or the presence or absence of other autoimmune disorders in the families. Patients with concurrent non-disabling extracerebellar symptoms were also included if cerebellar syndrome was the chief complaint.

Clinical Data and Neuronal Antibody Testing

The following data were collected: age at disease onset, sex, neurological symptoms, results of magnetic resonance imaging (MRI) scans, routine, oligoclonal bands (OB), and cytology of cerebrospinal fluid examination; concomitant malignancy and systemic autoimmune disease; serum autoantibodies such as thyroglobulin antibody (anti-Tg), thyroid peroxidase antibody (anti-TPO), Sjögren's syndrome A antibodies (anti-SSA) and Sjögren's syndrome B antibodies (anti-SSB), antinuclear antibody (ANA), and immunotherapy. Patients were followed regularly at the clinic or by telephone. Modified Rankin scale (mRS) was used to evaluate their neurological disabilities, with $mRS \leq 2$ at the last follow-up regarded as a good prognosis. Serum and CSF ACA antibody panel (Tr(DNER)/Zic4/ITPR1/Homer-3/neurochondrin/PKCγ/PCA-2/AP3B2/mGluR1/ATP1A3/CARPVIII/Rab6 antibodies) was examined using both a cell-based assay (CBA) and tissue-based assay (TBA) (EUROIMMUN, Lübeck, Germany), as previously reported [7, 8]. Paraneoplastic antibody assays (Hu/Yo/Ri/Ma2/Ta/CV2/ amphiphysin antibodies), autoimmune encephalitis antibodies (NMDAR/LGI1/GABAR/CASPR2/GAD65/IgLON5/DPPX antibodies), and antibodies against aquaporin protein-4 and gangliosides were also examined. Serum anti-gluten antibody (anti-endomysial and anti-gliadin IgG/IgA) testing, electromyography, screening for infection, toxins, metabolic diseases, and hereditary ataxia were also completed if clinically appropriate to exclude other causes.

Study Approval and Patient Consent

Informed consent was obtained from all individual participants or their deputies included in the study. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Peking Union Medical College Hospital (JS-891).

Table 1 Diagnostic criteria of PACA

1. Predominantly subacute or acute cerebellar syndrome (gait ataxia that may be associated with variable degrees of limb incoordination, dysarthria, nystagmus, diplopia) with or without additional non-disabling neurological abnormalities such as pyramidal sign and peripheral neuropathy/radiculopathy
2. MRI at presentation is usually normal or may show primarily cerebellar vermian atrophy with (if available) reduced MRS (NAA/Cr ratio) of the vermis
3. At least one of the following:
   3.1 At least two of the following:
   a. CSF pleocytosis and/or positive CSF-restricted IgG oligoclonal bands
   b. History of other autoimmune disorders or family history of autoimmune disorders in first-degree relatives
   c. Presence of antibodies that support autoimmunity but have not been shown to be either directly involved in ataxia pathogenesis or to be markers of ataxia with a known trigger (except cerebellum autoantibodies)[a]
   3.2 Presence of cerebellum autoantibodies (confirmed by TBA and/or CBA) that are not strongly paraneoplastic,[b] or immunofluorescence observed in TBA using cerebellar slices
4. Exclusion of alternative causes made by an experienced neurologist or ataxia specialist (including other causes of immune ataxia such as PCD and GA)

[a]Including thyroglobulin antibody, thyroid peroxidase antibody, Sjögren syndrome A antibodies, Sjögren syndrome B antibodies and antinuclear antibody.

[b]Including Zic4/ITPR1/Homer-3/neurochondrin/PKCγ/AP3B2/mGluR1/ATP1A3/CARPVIII/Rab6 antibodies.

CSF, cerebrospinal fluid; *CBA*, cell-based assay; *Cr*, creatine; *GA*, gluten ataxia; *IgG*, immunoglobulin G; *MRI*, magnetic resonance imaging; *MRS*, magnetic resonance spectroscopy; *NAA*, N-acetylaspartate; *PACA*, primary autoimmune cerebellar ataxia; *PCD*, paraneoplastic cerebellar degeneration; *TBA*, tissue-based assay.

Statistics

Statistical analyses were conducted using the Statistical Package for Social Sciences version 25.0. Given their non-normal distributions, data are expressed as the median with interquartile range (IQR), and the Mann–Whitney test was used for continuous variables. The Pearson χ^2 test or a Fisher's exact test was used for categorical variables. $P < 0.05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics

A total of 127 ACA patients were included, with 52 (40.9%) males. The mean age at onset was 45.8 (median 47.0, IQR 36.0–59.0) years. The mean disease duration (interval between cerebellar symptom onset and enrollment) was 10.6 (median 6.0, IQR 2.0–15.0) months. Symptom onset was acute (significant symptom progression within 2 weeks), subacute (2 weeks to 3 months), and chronic (longer than 3 months) in 28 (23.1%), 89 (73.6%) and 4 (3.3%) patients, respectively. The most common symptom was gait ataxia ($n = 124$, 97.6%), followed by limb ataxia ($n = 96$, 75.6%), dizziness ($n = 83$, 65.4%), dysarthria/dysphagia ($n = 75$, 59.1%), nystagmus ($n = 49$, 38.6%), and double vision ($n = 31$, 24.4%). In addition to cerebellar syndrome, pyramidal signs ($n = 36$, 28.3%) and peripheral neuropathy/radiculopathy ($n = 19$, 15.0%) were observed. Notably, these extracerebellar symptoms were associated with certain ACA subtypes. Three out of four OMS patients had pyramidal signs. Peripheral neuropathy/radiculopathy was absent in OMS, anti-GAD, and autoimmune encephalitis–associated CA, while presented in six out of nine MFS patients (Supplementary Table 1).

Twenty-three (18.1%) patients experienced prodromal symptoms (e.g., fever, cough, diarrhea) due to confirmed or presumed infection. While malignancy was identified in 28 (22.0%; lung cancer in 11, ovary cancer in 6, breast cancer in 4, and other types of cancer in 7) patients, 23 (59.0%) PCD patients were diagnosed with cancer by the end of the study. The other five patients with cancers included (1) one OMS patient, two anti-GAD–associated CA patient, and one autoimmune encephalitis–associated CA patient who also met the diagnostic criteria of PNS but were listed separately in the corresponding groups for clarity; and (2) one patient with thyroid papillary carcinoma. The diagnosis of PCD was not established because he was negative for onconeural antibody and thyroid papillary carcinoma was not usually related to PNS. He was diagnosed as PACA according to the criteria in Table 1. More than 40% PCD patients were tumor-free. They were classified as PCD based on the presence of high-risk antibodies, high-risk phenotypes and/or follow-up < 2 years, resulting in a PNS-Care score for "probable PNS."

Neuronal Antibodies and Nosology

As shown in Table 2 and Fig. 1, PACA ($n = 48$, 37.8%, with 14 and 34 patients meeting the original and modified diagnostic criteria, respectively) and PCD ($n = 39$, 30.7%) were the dominant ACA subtypes. Together, neuronal antibodies were detected in 86 (67.7%, 69 in paired serum and CSF samples, 4 in serum only, sample type unavailable in the other 13) patients, with positive ganglioside antibodies in another 4 patients. All PCD patients were positive for high-risk paraneoplastic neurological antibodies.

Laboratory and MRI Characteristics

Examination of systemic autoantibodies revealed that 27 (21.3%) patients were anti-SSA/SSB positive, 16 (12.6%) (including six with Hashimoto's thyroiditis) were anti-TPO/Tg positive, and another 11 (8.7%) were positive for both antibodies. Another 9 (7.1%) patients were ANA-positive, but anti-SSA/SSB-negative. Besides Hashimoto's thyroiditis, other concomitant systemic autoimmune diseases included Sjögren's syndrome ($n = 12$), vitiligo ($n = 3$), Behcet's disease ($n = 2$), and rheumatoid arthritis ($n = 1$).

The median white blood cell (WBC) count and mononuclear cell percentage of CSF were 5 (IQR 2–20)/uL and 98.6% (IQR 87.0–100%), respectively. The median CSF protein concentration was 0.47 (IQR 0.36–0.71) g/L. Of the 113 patients with CSF WBC data, 59 (52.2%) were within the normal limit (WBC 0–5/uL). In patients with CSF pleocytosis, the median WBC count was 20 (IQR 9.5–60.3, range 6–220) /uL and mononuclear percentage 95.0% (IQR 87.0–100%, range 50–100%), in line with predominant lymphocytic inflammation in cytology. CSF-restricted OB was positive in 46 of 90 (51.1%) specimens. Among the 88 patients with CSF data on OB and WBC, 25 (28.4%) were normal for both examinations.

Of the 115 patients who underwent brain MRI, the results were normal or showed nonspecific white matter changes in 64 (55.7%). Twelve (10.4%) patients had cerebellar atrophy and 9 (7.8%) showed atrophy including but not limited to the cerebellum. MRI lesions were noted in 30 (26.1%) patients, including exclusive cerebellar involvement in six. The remaining 24 patients had concurrent hippocampus/medial temporal lobe ($n = 8$), pyramidal track ($n = 3$), cerebrum ($n = 3$), or multiple ($n = 10$) lesions (see Supplementary material and reference [9] for sample figures). The brain MRI characteristics of each ACA subtype are summarized in Supplementary Table 1.

Table 2 ACA subtypes and neuronal antibodies

ACA subtype	Neuronal antibodies	No	ACA subtype	Neuronal antibodies	No
PCD[a]		39	PACA		48
	anti-Yo	12		anti-Homer-3	4
	Anti-Tr	4		anti-neurochondrin	3
	anti-Hu	4		anti-CARPVIII	1
	anti-CV2	3		anti-mGluR1	1
	anti-Amphiphysin	3		anti-Zic4	1
	anti-SOX1	3		anti-Rab6A/Rab6B	1
	anti-PCA2	3		TBA +	8
	anti-Ma2	2		Neuronal Ab-negative	29
	anti-Ri	1	Autoimmune encephalitis associated CA		16
	multiple neuronal Abs	4		anti-NMDAR	12
MFS		9		anti-CASPR2	2
	anti-GD1b	2		anti-DPPX	1
	anti-GQ1b	2		anti-GABAR	1
	Neuronal Ab-negative	5	OMS		4
Anti-GAD associated CA		11		anti-amphiphysin & anti-Ri	1
	anti-GAD	11		Neuronal Ab-negative	3

[a]One OMS patient, two anti-GAD–associated CA patient and one autoimmune encephalitis–associated CA patient that also met the diagnostic criteria of paraneoplastic neurologic syndromes were listed separately in the corresponding groups.

ACA, autoimmune cerebellar ataxia; *CA*, cerebellar ataxia; *GAD*, glutamic acid decarboxylase; *MFS*, Miller Fisher syndrome; *OMS*, opsoclonus-myoclonus syndrome; *PACA*, primary autoimmune cerebellar ataxia; *PCD*, paraneoplastic cerebellar degeneration.

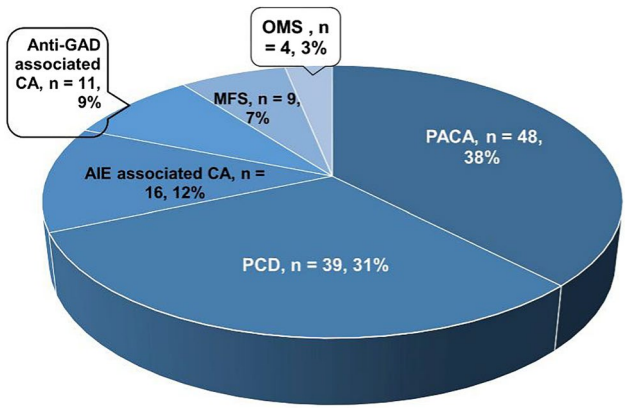

Fig. 1 Composition of ACA case series. ACA, autoimmune cerebellar ataxia; AIE, autoimmune encephalitis; CA, cerebellar ataxia; GAD, glutamic acid decarboxylase; MFS, Miller Fisher syndrome; OMS, opsoclonus-myoclonus syndrome; PACA, primary autoimmune cerebellar ataxia; PCD, paraneoplastic cerebellar degeneration

Treatment and Prognosis

The mean interval between symptom onset to start of immunotherapy was 113 (median 46, IQR 18–156) days. Acute phase treatment included intravenous immunoglobulin (IVIg, $n = 16$, 12.6%), pulse corticosteroid therapy ($n = 14$, 11.0%), oral corticosteroid ($n = 11$, 8.7%), and IVIg combined with corticosteroid ($n = 65$, 51.2%). Twenty-one (16.5%) patients received neither IVIg nor corticosteroid therapy. Surgery, chemotherapy, or radiotherapy was applied to 17 patients to treat the malignant tumor. Mycophenolate mofetil was prescribed to 29 (22.8%) patients as long-term immunotherapy. Various immunosuppressants including cyclophosphamide, azathioprine, methotrexate, hydroxychloroquine, and rituximab were used in another 10 (7.9%) patients.

The mean follow-up time from registration was 28.2 (median 24.0, IQR 3.0–45.0) months, with 15 (11.8%) patients lost to follow-up. Mean mRS at the last follow-up was 2.88 (median 3.0, IQR 1.0–4.0). The prognosis was good in 53 (47.3%) patients (mRS at the last follow-up ≤ 2). Thirteen (10.2%) patients died, due to malignancy in eight patients, complications of neurological abnormalities in two, and cause not available in three (including two PCD patients and one patient with autoimmune encephalitis–associated cerebellar ataxia). Symptom relapses or immunotherapy dependence were seen in 24 patients.

Comparison of PCD with PACA

As shown in Table 3, compared with PACA, PCD patients had a significantly older onset age, and higher ratio of coexisting malignancies. PACA patients were more likely to experience prodromal cough/diarrhea/fever, and to have concurrent systemic autoimmune diseases and related

Table 3 Comparison between PCD and PACA

	PCD ($n=39$)	PACA ($n=48$)	P value
Male/no. (%)	18 (46.2)	14 (29.2)	0.102
Age at onset/years	56.0 (47.0, 59.0)	44.0 (24.3, 57.8)	**0.004**
Disease duration/months	7.0 (3.0, 19.0)	5.0 (1.0, 9.8)	**0.050**
Malignancy/no. (%)	23 (59.0)	1 (2.1)	**< 0.001**
Systemic autoantibodies[a]/ no. (%)	13 (33.3)	31 (64.6)	**0.004**
Systemic autoimmune disease[b]/no. (%)	3 (7.7)	13 (27.1)	**0.020**
Prodromal symptoms[c]/no. (%)	0 (0)	14 (29.2)	**< 0.001**
Treatment			
Pulse corticosteroid therapy/no. (%)	8 (20.5)	27 (56.3)	**0.001**
Oral corticosteroid/no. (%)	18 (46.2)	18 (37.5)	0.415
IVIg/no. (%)	20 (51.3)	33 (68.8)	0.097
MMF/no. (%)	6 (15.4)	13 (27.1)	0.189
Follow-up time/months	20.0 (2.8, 43.5)	23.0 (2.3, 40.5)	0.758
mRS at last follow-up	4.5 (3.8, 6.0)	2.0 (1.0, 4.0)	**< 0.001**

[a]Including anti-thyroglobulin, anti-thyroid peroxidase, anti-Sjögren syndrome A, anti-Sjögren syndrome B and antinuclear antibody.

[b]Including Sjögren syndrome, Behcet's disease, vitiligo and rheumatoid arthritis.

[c]Including fever, cough, rhinorrhea and diarrhea.

IVIg, intravenous immunoglobulin; *MMF*, mycophenolate mofetil; *mRS*, modified Rankin scale; *PACA*, primary autoimmune cerebellar ataxia; *PCD*, paraneoplastic cerebellar degeneration.

autoantibodies. MRS at last follow-up was significantly higher in the PCD group than in the PACA group, indicating a worse prognosis. The ratios of neurological presentations (e.g. dizziness, gait ataxia, limb ataxia, pyramidal sign, peripheral neuropathy/radiculopathy), results of CSF examinations (e.g., WBC count and classification, protein concentration, and OB) and brain MRI were not significantly different between the two groups (Supplementary Table 2).

Discussion

We report 127 patients with ACA with different etiology. To our knowledge, this study is the largest ACA case series from China and provides several relevant findings: (1) PCD and PACA were the major subtypes of ACA; (2) a considerable portion of ACA patients had symptoms or neuroimaging findings suggesting extracerebellar involvement; (3) more than 20 types of neuronal antibodies were detected in two-thirds patients, while CSF pleocytosis and OB were each seen in about half of the patients; and (4) compared with PCD, PACA patients were younger, more likely to have concurrent systemic autoimmune disease or systemic autoantibodies, and had a better outcome.

Comparable to previous studies, PCD and PACA were the dominant ACA subtypes in our patients; therefore, malignancy screening would be an important topic for ACA patient management [10, 11]. However, the two subtypes were almost indistinguishable in terms of neurological phenotype, CSF parameters, and brain MRI features. Although our study suggested that a younger onset age, the presence of prodromal symptoms, and systemic autoimmune antibodies or autoimmune diseases might support the diagnosis of PACA, these were neither specific nor straightforward. Thus neuronal autoantibody detection and malignancy screening are important to establish a diagnosis. On the other hand, in terms of the association between antibody and malignancy, our results suggested that in patients with less well-characterized cerebellar antibodies defining PACA, seldom had malignancy been detected during follow-up. Therefore, neuronal antibody testing may guide malignancy screening approaches in ACA patients.

As a major ACA type in Caucasian populations, GA has rarely been reported in mainland China [1]. Although previous studies demonstrated the relationship between GA autoantibodies and ataxia in Chinese patients, and scattered GA cases have been reported, in our ACA case series we did not identify any GA case [12, 13]. Occasionally, we detected a few cerebellar ataxia patients with celiac disease-related antibodies, but they all lacked typical GA manifestations or abdominal symptoms, and their ataxia did not improve after a gluten-free diet, the effectiveness of which provides evidence for GA diagnosis [14–18]. Future studies may clarify the epidemiological and clinical characteristics of GA in Chinese populations.

Post-infectious cerebellitis (PIC) is mediated by an abnormal autoimmune process triggered by infection, most commonly varicella, and tends to affect younger children [2]. In

this study, we did not list this category separately because (1) the infection-like symptoms were usually mild and self-limiting, such that patients usually did not seek medical attention, and a specific pathogen was seldom identified; (2) compared with other PACA patients, those with prodromal infection-like symptoms had similar neurological presentations, CSF, and brain MRI characteristics and prognoses (data not shown); (3) four patients with infection-like prodrome were also positive for neuronal antibodies, including mGluR1, Homer-3, neurochondrin, and Zic4 antibodies, suggesting that PIC and PACA were not mutually exclusive categories, but could overlap. The question of whether such prodrome was the presentation of infection or of immune activation has also been raised previously [19]. Therefore, we decided to focus on neuronal antibodies, which are more specific diagnostic markers, and not include PIC as a separate category in this study.

In this case series, 12.5% of ACA patients had coexisting autoimmune encephalitis mediated by antibodies against neuronal surface proteins, mostly anti-NMDAR. Similarly, cerebellum involvement in anti-NMDAR encephalitis has been reported previously, and could be the initiating or even major symptom, mostly in young children whereas relatively rare in adults [20–22]. In cohort studies, ataxia was observed in 5% and MRI abnormalities in cerebellum in 6% of anti-NMDAR encephalitis patients [23, 24]. However, cerebellar and cerebral involvement could show different prognoses: the former is usually irreversible and related to unfavorable outcomes, whereas diffuse cerebral atrophy tends to be reversible and does not imply a poor prognosis [25]. This disassociation of natural course indicates that ACA might be a concomitant neurological autoimmunity, rather than the intrinsic phenotype of anti-NMDAR encephalitis.

Some ACA patients in this study had neurological symptoms in addition to cerebellar syndrome (e.g., pyramidal sign, peripheral neuropathy). Meanwhile, brain MRI could show abnormalities beyond cerebellar atrophy. The diverse clinical and imaging characteristics have also been noted previously [10, 11, 26]. Even ACA patients related to the same cerebellum autoantibodies can have different neurological syndromes, such as those with anti-Homer-3 [9]. This phenotypical heterogeneity may indicate a widespread aberrant immune process, as suggested by the extensive binding of cerebellum autoantibodies to multiple structures of the nervous system in TBA studies [3, 27, 28].

In this study, neuronal antibodies were detected in 67.7% (86/127) of the subjects, and 19 of 48 PACA patients had cerebellum autoantibodies confirmed by TBA and/or CBA. Although their pathogenesis needs further research, neuronal antibodies offer important clues for an autoimmune etiology, especially when investigations for CSF and systemic autoimmune diseases are negative, and warrant timely immunotherapy [3]. Therefore, neuronal antibody testing should be conducted in patients with possible ACA; ideally with TBA using mouse or rat brain performed simultaneously.

ACA can present with an initial relapsing course [29, 30]. In our series, relapse were observed in 18.9% (24/127) of the patients, including PCD patients who are usually believed to benefit little from immunotherapy [31]. Therefore, paraneoplastic etiology cannot be excluded if immunotherapy is effective. Additionally, since relapse is not uncommon for ACA patients, particularly during the weaning off corticosteroids or after the IVIg treatment is over, long-term immunotherapy should be considered for patients with relapse.

The PCD patients in this study had a significantly poorer outcome than PACA patients, even after exclusion of deceased subjects whose death was mainly due to malignancy (Supplementary Table 2). This result is in line with a previous study and suggests the importance of timely diagnosis and treatment of the underlying tumor [10, 11]. In this study, infection-like prodromes were significantly more common in PACA than in PCD patients. Preceding vestibular or brainstem symptoms involving vertigo, nausea, and vomiting have been reported previously before manifested cerebellar ataxia in PCD [26, 32, 33]. Fever and other infectious-like prodromes were noted occasionally, such as in patients with anti-mGluR2 and anti-Tr [29, 34]. However, we did not observe antedated infectious-like manifestations in this study, possibly due to recall bias related to its retrospective nature.

This study has some limitations. First, it is a single-center study, and our department mainly focused on adult patients, which can lead to some bias. Second, detailed cerebellar symptoms evaluation such as the Scale for the Assessment and Rating of Ataxia score were lacking in some patients. Third, few patients were tested for gluten antibodies and none received duodenal biopsy or had more specific GA autoantibodies tested. In the future, a multi-center prospective study with thorough cerebellar function assessment and a well-established GA diagnosis process will be helpful for more comprehensively depicting the spectrum and prognosis of ACA.

Conclusion

This study reported a large ACA case series from China. Extracerebellar neurological involvement was common, and various cerebellum autoantibodies were detected. PCD and PACA were the dominant ACA subtypes. Although PCD patients were older and had poorer outcomes, the neurological syndromes, characteristics of CSF analyses, and brain MRI were not significantly different. The identification of cerebellum autoantibodies is useful for diagnosis and guides malignancy screening.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12311-022-01412-5.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

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