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SHORT REPORTS

Neurochondrin Antibody Serum Positivity in Three Cases of Autoimmune Cerebellar Ataxia

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Abstract

To report three cases of autoimmune ataxia patients with positive neurochondrin (NCDN) antibodies. Patients with unknown cerebellar ataxia were screened for autoimmune cerebellar ataxia (ACA)-related antibodies, including glutamic acid decarboxylase 65 (GAD65), delta/notch-like epidermal growth factor-related receptor (Tr/DNER), zinc finger protein 4 (ZIC4), inositol 1,4,5-triphosphate receptor 1 (ITPR1), Homer protein homologue 3 (Homer-3), neurochondrin (NCDN), Purkinje cell antibody 2 (PCA-2) and carbonic anhydrase-related protein VII (CARPVII). The antibodies were assessed by indirect immunofluorescence using transfected cells (cell-based assay, CBA) and monkey cerebellum (tissue-based assay, TBA) with the multi-antigen co-plate biochip mosaic technique. Patients with positive antibodies received immunotherapy and were followed up in the clinic. Clinical characteristics, laboratory data, and outcomes of antibody-positive patients were described, analysed and compared with previously reported cases. The NCDN antibody was positive in three male patients in whom the onset ages were four years and 11 months, two years and seven months and 67 years old. Serum antibody titres were 1:32, 1:100 and 1:320. Cerebral ataxia was the most prominent presentation. Cerebellar atrophy was found in one of the patients. Immunotherapy was effective in all three patients. The NCDN antibody is associated with autoimmune ataxia, and it has been suggested that the NCDN antibody should be tested in patients with cerebellar ataxia who are negative for routine ACA antibodies. Early immunotherapy may have a beneficial impact on prognosis.

Keywords Neurochondrin · NCDN · Autoimmune · Cerebellar · Ataxia

Introduction

Autoimmune cerebellar ataxia (ACA) is a group of acquired autoimmune diseases characterized by cerebellar symptoms. At present, about 30 types of antibodies related to ACA have been reported. Paraneoplastic cerebellar degeneration (PCD) is a well-known autoimmune disorder of the cerebellum, characterized by the presence of specific autoantibodies against the associated neoplasm, such as anti-Yo, anti-CV2/CRMP5 and anti-Hu. The clinical entity of non-paraneoplastic immune-mediated cerebellar ataxias (CAs) was established recently, and related antibodies include anti-transglutaminase 2,6 and anti-glutamic acid decarboxylase (GAD). With progress in experimental techniques, some new types of neuroantibodies associated with ACA have been reported, including metabolic glutamic acid receptor 1 (mGluR1), Homer protein homologue 3 (Homer-3), voltage-gated calcium channel (VGCC), Purkinje cell antibody 2 (PCA-2) [1–3], anti-caspr2 [4], anti-TRIM9 and TRIM 67 [5], resulting in more patients being diagnosed and receiving suitable treatment. In 2016, Ramona Miske and colleagues first reported ACA cases associated with neurochondrin (NCDN) antibodies [6]. Since 2017, we have employed a novel ACA antibody kit that includes the NCDN antibody to screen patients with unexplained cerebellar ataxia. Three cases with positive NCDN

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antibodies were found. This study describes the clinical and laboratory features, treatment and outcome of these 3 patients. This is the first such cohort report of cases treated in China.

Materials and Methods

Study Population

This study was performed in four hundred patients with unidentified cerebellar ataxia. Patients with a family history of ataxia were excluded. Other inclusion criteria were as follows: patients tested negative for an autoimmune encephalitis antibody profile (NMDAR, LGI1, GABAR, CASPR2, AMPA1, AMPA2, DPPX) and a paraneoplastic antibody profile (Hu, Yo, Ri, Cv2, Ma2, and amphiphysin). A clinical evaluation, immunotherapy and follow-up were performed. All patients or patient guardians provided written informed consent for the clinical assessment and registration according to the registration project for encephalitis and paraneoplastic neurologic syndrome (medical ethics committee approval number JS-891).

ACA Antibody Detection Profile

The kit was co-customized by the Neurological Laboratory of Peking Union Medical College Hospital and the EUROIMMUN Lhe Ki Medical Laboratory of Germany. This ACA antibody spectrum includes GAD65, Tr (DNER), ZIC4, ITPR1, Homer-3, NCDN, PCA-2 and CARPVII, which were detected by indirect immunofluorescence using transfected cells (CBA) and monkey cerebellum (TBA) with the multi-antigen co-plate biochip mosaic technique.

The test steps were performed, as recommended in the kit, as follows: 30 μL of the serum or plasma (dilution fold 1:10) or cerebrospinal fluid (original sample) was added to the reaction zones of the sample plate, and slides containing thin slices of the biological substrates were then placed onto the plate. The slides were incubated for 30 min at room temperature, flushed with phosphate buffer solution, and incubated with 25 μL of sheep anti-IgG labelled with FITC for 30 min at room temperature. They were then rinsed with PBS and observed under a fluorescence microscope.

Results

Clinical Characteristics

Four hundred patients were included in this study, and, of these, 3 patients tested positive for anti-NCDN Ab. Only serum samples were tested in patient 1 and patient 2. Both serum and cerebrospinal fluid (CSF) were tested in patient 3.

Patient 1

The patient was a boy with an age of 5 years and 2 months who was admitted to Beijing Children's Hospital with progressive dysarthria and gait instability for 3 months. When he was 5 years and 4 months old, he could no longer walk by himself. On physical examination, volitional tremor and dysmetria were notable. His perinatal history, family history and past history were unremarkable. MRI of the brain and spinal cord indicated significant cerebellar atrophy (Fig. 1) and was otherwise unremarkable. A repeated MRI performed 5 months later was identical to the previous MRI. EEG was insignificant.

Tumour screening including abdominal and lung CT, abdominal B and testicular ultrasound and blood tumour markers (HCG, AFP, CEA, and NSE) were negative. Serum and CSF screening tests for infection, including TORCH IgM, EBV IgM and IgG and CSF smears submitted to Gram, acid-fast and ink staining were negative.

Blood and urine amino acid and organic acid analyses were negative, and whole-exon sequencing and SCA fragment analysis were negative, suggesting no genetic cause.

Immune-related indexes of ANA and anti-dsDNA, thyroid function, thyroid antibody, normal range of T cell subsets and blood IgM, IgG and IgA were unremarkable.

CSF analysis showed that glucose, chloride and lactic acid levels were normal, with CSF glucose/blood glucose at 0.61 (normal). CSF cytology was unremarkable and negative for the oligoclonal band (OB). However, the patient tested serum-positive for NCDN Ab with a titre of 1:32.

In the following 2 months, his symptoms progressed, and he became unable to walk on his own (mRs = 3). Thus, immunotherapy was administered (eight months after onset) with IVIG (2 g/kg) and methylprednisolone (MP) (20 mg/kg/d × 3 d) infusion, followed by oral prednisone sequential therapy and a gradual reduction in dosage. The total course of corticosteroid treatment was five months. After two weeks of immunotherapy, the symptoms improved. After one month of treatment, the child could walk alone, his step base was wide, his language was clear and his tremor had improved (mRs = 1). However, after five months of treatment, his condition did not continue to improve.

Patient 2

Patient 2 was a preschool boy who was admitted to Beijing Children's Hospital because of recurrent ataxia for one year.

First episode: In March 2016, the boy (2 years and 7 months old) had acute onset of fever, with the highest temperature reaching 39.3 °C. After two days, gait instability was noticed,

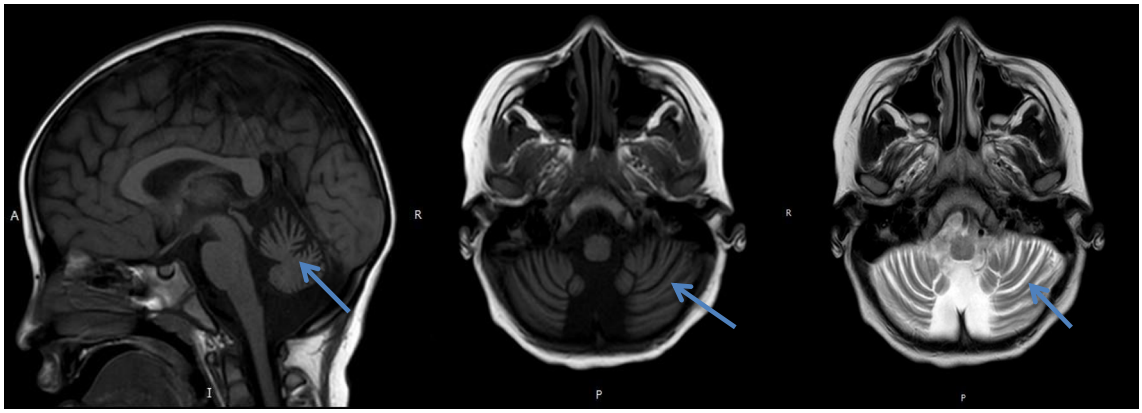

Fig. 1 Cranial MRI showing remarkable cerebellar atrophy (arrow)

and he could not hold his head erect. He also exhibited mild dysphagia and dysarthria. He then received IVIG (2 g/kg) and low-dosage oral prednisone for two weeks. Two days after treatment, his condition began to improve gradually. Ten days later, the boy recovered completely.

Second episode: In December 2016, the boy (then 3 years and 4 months old), after having a fever (the highest temperature reaching 38.8 °C) for two days, showed an imbalanced gait as well as blurred speech and could not even sit unaided. After eight days, his right upper limb was clumsy and his right hand could not stretch. Intentional tremor and dysmetria spread to both hands. A physical examination indicated decreased muscle tension and strength and a disappeared deep tendon reflex. The patient again received IVIG (2 g/kg) for 2 weeks with an extended course of corticosteroid for 2 weeks. The child recovered gradually, almost returning to his original condition except for a slight tremor in the right hand and a mild unsteady gait.

Third episode: In March 2017 (3 years and 7 months old), instability in walking appeared again after two days of fever and gradually aggravated. The clinical presentation was similar to the second episode, except that the dysarthria and ataxia were more serious. Intelligence was normal during all of the disease episodes.

The boy's perinatal history was normal, but he had mild motor retardation before onset. He turned over by nine months, could sit unaided by ten months and walked by 15 months. His father presented with "fever and weakness" when he was six years old and then recovered, with minor sequelae remaining. There were no abnormalities on cranial and spinal cord MRI. Routine laboratory tests, including the infection index, immune-related index and a metabolic screen, were not remarkable. A tumour screen was also negative, including abdominal and lung CT; abdominal B ultrasound was carried out to search potential associated cancer, particularly neuroblastoma. In addition, electromyography (EMG), electroencephalogram (EEG), somatosensory-evoked potential (SEP), visual-evoked potential (VEP) and auditory brainstem response (ABR) were all normal. The patient tested serum-positive for NCDN Ab with a titre of 1:100.

The mRS was 4 before treatment at the third episode. IVIg, MP and rituximab (375 mg/m^2 × 6 times) infusions were given successively and were followed by oral prednisone. After treatment for one month, the patient's condition gradually improved, especially after the application of rituximab. He was followed up for one year and six months after the third episode. Mild motor disturbance remained and presented as slightly unstable running, incongruous posture and slower speech. Cognition and intelligence were normal. The mRS was 1 at the last follow-up.

Patient 3

A 67-year-old man was admitted to Peking Union Medical College Hospital with intermittent dizziness and unstable walking for three months.

First episode: In January 2018, one week after an upper respiratory tract infection, the man had dizziness with nausea and mild walking instability. He felt drunk. No therapy was implemented, and the symptoms then resolved completely after one week.

Second episode: In February 2018, dizziness and walking instability similar to the first episode emerged again without any preceding event. The symptoms disappeared spontaneously one week later.

Third episode: In March 8, 2018, the same symptoms as previously mentioned appeared again but gradually aggravated. After one month, the patient could not even walk alone, and his speech was not as clear or fast as before. A physical examination showed horizontal nystagmus and trunk ataxia signs. Right upper limb muscle strength was IV, and bilateral Achilles tendon reflex reduced. He had a history of hypertension for 20 years and hyperlipidaemia for one year. He also had drinking history for 30 years, but he had been abstinent for five years. The family history showed coronary heart disease (father, mother, younger brother and younger sister).

A cranial MR showed scattered obsolete ischaemic lesions and no cerebellar atrophy. A tumour-related examination included lung CT, abdominal CT, abdominal B ultrasound, thyroid ultrasound, PET-CT and tumour markers, including CEA, CA242, and CA19-9, which were all negative. Metabolic indicators, including serum folic acid, vitamin B12, homocysteine and ceruloplasmin, were all normal. Infection indexes, such as TORCH, HIV, HBV, HCV and *Treponema pallidum*, were negative. ANA, anti-dsDNA and ENA were negative. The CSF leukocyte count was 11×10^6 cells/L, and the mononuclear cell count was 6×10^6 cells/L. The CSF OB was suspicious positive, and the CSF cytology suggested mild lymphocytic inflammation. The patient tested serum-positive for NCDN Ab with a titre of 1:320 and serum-negative in CSF.

The patient received only an IVIG infusion (2 g/kg). After four days of treatment, an improvement was observed, his dizziness was relieved, and the instability in walking was alleviated. His handwriting became neater than it was before treatment. The mRs improved from 3 before treatment to 2 after treatment.

Antibody Detection Results

The patient was seropositive for the NCDN antibody in three of the cases, although CSF tested negative in patient 3. The serum antibody titres were 1:32, 1:100 and 1:320 in cases 1, 2 and 3, respectively. The samples were sent to EUROIMMUN Lübeck Medical Laboratory for verification, and the same results were obtained.

The positive serum NCDN antibody test obtained in the third patient demonstrated fine grainy fluorescence in the cell layer and molecular layer of the monkey cerebellum granules. There was a positive reaction for the NCDN antibody in the transfected cells (Fig. 2).

Discussion

Autoimmune cerebellar ataxia (ACA), also called autoimmune cerebellitis or immune-mediated cerebellar ataxia (iMCA) [7], is one of the main causes of acquired cerebellar ataxia. In addition to the well-established concept of paraneoplastic cerebellar degeneration(PCD), the clinical entity of non-paraneoplastic immune-mediated cerebellar ataxias was recently established [8]. Because of its treatability and reversibility, ACA is particularly important in the differential diagnosis of hereditary cerebellar ataxia.

ACAs are characterized by their association with autoantibodies, but whether these autoantibodies are the cause or result of the IMCAs remains a matter of debate [9]. In recent years, the discovery and application of a series of ACA-related antibodies has provided a laboratory basis for the diagnosis of ACA. In 2015, a review entitled "Medusa-head ataxia" by professors *Jarius* and *Wildemann* was published in *The Journal of Neuroinflammation*. ACA and its related antibodies were elaborated in detail. When tested by immunohistochemistry (IHC) in cerebellum tissue sections, these antibodies show a staining pattern resembling a Gorgon's head that is caused by binding of IgG to Purkinje cell (PC) somata and dendrites and is therefore often referred to as a "Medusa head" antibody reaction [1–3]. The anti-NCDN antibody is a new type that extends the "Medusa head" antibody spectrum.

Neurochondrin is specifically expressed in neurons in a somatodendritic distribution pattern. It is a 75-kDa protein with an amino acid identity of approximately 98% among rat, mouse and human orthologous proteins [10]. In the adult rodent brain, neurochondrin is highly expressed in the cerebellum, amygdala and hippocampus and is more moderately expressed in the striatum and cortex [11].

Some studies have verified the interaction between NCDN and G protein-coupled receptors, such as metabotropic glutamate receptors (mGLuR1 and mGLuR5), which are associated with the regulation of long-term synaptic plasticity in the cerebellum and hippocampus [12].

In 2016, Ramona Miske and colleagues reported three adult patients with subacute or chronic progressive autoimmune ataxia related to the NCDN antibody. They found that during the active but not the residual state of the disease, B cells and plasma cells, activated CD41 and CD81 T cells and B cell-derived NCDN antibodies accumulated in the CSF

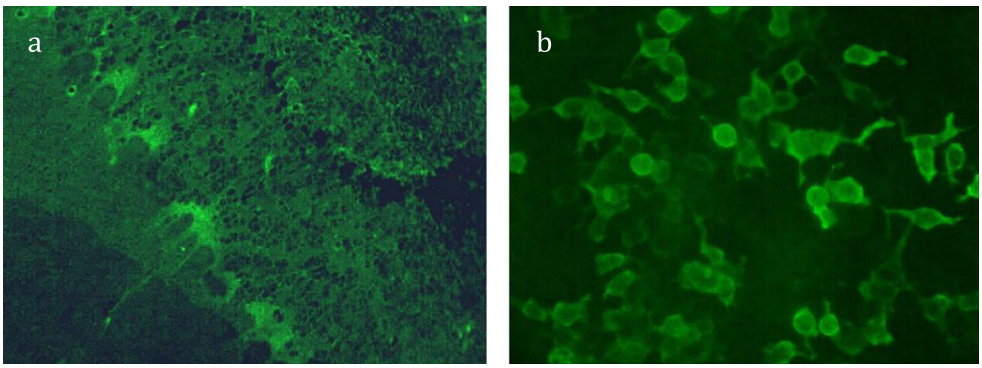

Fig. 2 Patient 3 serum NCDN antibody detection. **a** A fine granular fluorescence reaction within the granular cell layer and molecular layer of the monkey cerebellum (×200). **b** Neurochondrin (NCDN) antibody detection: NCDN-transfected cells were positive (CBA, indirect immunofluorescence) (×200)

compartment. The antigen-driven activation of CD81 T cells and CD41 T cells also occurred in the peripheral immune compartment, suggesting an accompanying antigen-specific T cell response is an underlying effector mechanism [6].

Our study is the second report (after Ramona Miske's report) on autoimmune ataxia related to NCDN antibodies. These two articles involved a total of 6 patients. The data are summarized in detail in Table 1. They have the following clinical characteristics: (1) Cerebellar syndrome was the main manifestation, and axial ataxia manifested as imbalanced gait imbalance and dysarthria were probably more prominent. Axial ataxia was the onset presentation of P1 and P2 and limb ataxia appeared gradually and aggravated with the progress of disease, while P3 mainly manifested as trunk ataxia, and the symptoms of limb ataxia were mild. (2) Nystagmus, dysphagia and dysmetria occurred in most cases. Other signs, including weakness, abnormal muscular tension and tendon reflex, were found in some cases. (3) Cerebellar atrophy was observed in some patients (4/6). (4) In all, 50% (3/6) of cases exhibit CSF inflammatory changes. (5) Although NCDN is also expressed in the cerebral cortex, no cortical symptoms, such as convulsions and disturbance of consciousness, are involved, and this may be one of the clinical features of the disease. (6) No tumours were found in any of the cases. (7) The three previously reported patients were monophasic, but two of our patients had recurrence (patients 2 and 3). The two patients appeared to show other common features, including the preceding of infections, no cerebellar atrophy showed in MRI and good response to immunotherapies. These features were not described in previously reported cases. We speculate possible reasons as follows: (1) They received timely treatment in the early stage of the disease. (2) There might be a heterogenic phenotype of ACA associated with anti-NCDN antibody.

Currently, most cases of ACA are adults, and children are very rarely affected. This study included two children, the youngest with an age of onset of younger than 3 years old. The two paediatric patients had lower antibody titres than were found in the adults (P3, P4, P5 and P6), but there was no obvious difference in clinical features. In 2017, Frank reported a case of a child with chorea related to the NCDN antibody who had no ataxia presentation [13]. The patient responded very well to clinical treatment by immunotherapy, but no further research on the mechanism has been carried out.

Despite the identification of an increasing number of immune-mediated cerebellar ataxias, there is no proposed

Table 1 Features of ACA patients with NCDN-antibody serum-positive in our and Ramona Miske's studies

		P1	P2	P3	P1'	P2'	P3'
Onset age		4 y 11 m	2 y 7 m	67 y	51 y	23 y	19 y
Sex		M	M	M	M	M	F
Duration at first visit		3 m	12 m	3 m	21 m	54 m	120 m
Symptoms		M	R	R	M	M	M
Clinical features	Dizziness	–	–	+	NM	+	+
	Imbalance	+	+	+	+	+	+
	Dysarthria	+	+	+	+	+	+
	Nystagmus	–	–	+	+	–	+
	Bucking/dysphagia	–	+	+	NM	NM	+
	Tremor/dysmetria	+	+	–	NM	+	+
	Muscular tension	Hypo	Hypo	Hyper	NM	NM	NM
	Tendon reflex	+	–	–	NM	NM	NM
	Weakness	–	+	+	NM	NM	NM
Cerebellar atrophy		+	–	–	+	+	+
CSF inflammatory changes		–	–	+	+	+	–
Serum anti-NCDN		1:32	1:100	1:320	1:320	1;320	1:1000
CSF anti-NCDN		ND	ND	–	1:32	1:1	1:32
Immunological drugs		IVIG, MP	IVIG, MP, RIT	IVIG	MP, CTX, RIT, IVIG, PE, IA	MP, PE, IA, TB, FP, CTX	PE, MP, IFNβ, MIT, AZA, IVIG
Follow-up		IP	IP	IP	IP	IP	SB
Conjectured effective drugs		IVIG, MP	IVIG, MP, RIT	IVIG	CTX	CTX	AZA, IVIG

P, patients in our study; P′, patients in Ramona Miske's study

RIT, rituximab; MP, methylprednisolone; PE, plasma exchange; IA, immunoadsorption; TB, tetrabenazine; FP, fampridine; CTX, cyclophosphamide; IFN, interferon; MIT, mitoxantrone; AZA, azathioprine; IVIG, intravenous immune globulin; R, recurrent; IP, improved; M, monophasic; SB, stable; ND, not done; NM, not mentioned

standardized therapy. The main therapy includes the removal of autoimmune triggering factors (e.g. gluten or cancer) and immunotherapy (e.g. corticosteroids, intravenous immunoglobulin, immunosuppressants) with adaptation according to each subtype [9].

Because of the rarity of NCDN antibody-related ACA cases, there is no consensus on immunotherapy. The three patients reported by Ramona Miske were not responsive to most immunotherapy, and only a few drugs, such as cyclophosphamide, were effective. Our patients had a rapid and obvious response to immunotherapy, even single IVIG treatment (P3). A possible reason was the shorter disease course in our patients. In 2018, Professor Mitoma proposed "Time is Cerebellum" as a principle in the management of patients with cerebellar diseases, especially immune ataxias, the complexity of which often delays therapeutic intervention [14]. Therefore, we suggest that NCDN antibody detection should be carried out in ataxic patients who are negative for common antibodies to diagnose and intervene as early as possible as this might be beneficial for prognosis.

We acknowledge some obvious limitations of our study. First, two patients (patients 1 and 2) were not tested for anti-NCDN antibodies in the CSF, and there was no successive monitoring of antibodies during the follow-up process. Second, the assessment of cellular and humoural immune functions in patients was insufficient. Third, some patients were followed up for only a short time. The above-mentioned problems need to be considered in future research.

Conclusion

The NCDN antibody is a novel antibody associated with autoimmune ataxia, and NCDN antibody-positive ACA is mainly characterized by cerebellar ataxia, while symptoms of encephalopathy are not prominent. No paraneoplastic cases were found. Cranial MR may show cerebellar atrophy, which can occur in all age groups, including children. At present, the limited data show that men are more often affected than women and that immunotherapy is effective in some patients. It is necessary to detect ACA-related antibodies in cerebellar ataxia patients with unknown aetiology to achieve an early diagnosis and implement immunotherapy to improve patient prognoses.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. Jarius S, Wildemann B. "Medusa-head ataxia": the expanding spectrum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part 1: anti-mGluR1, anti-Homer-3, anti-Sj/ITPR1 and anti-CARP VIII. J Neuroinflammation. 2015;12:166.
2. 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-delta2, anti-Ca/ARHGAP26 and anti-VGCC. J Neuroinflammation. 2015;12:167.
3. 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.
4. Do LD, Gupton SL, Tanji K, Bastien J, Brugière S, Couté Y, et al. TRIM9 and TRIM67 are new targets in paraneoplastic cerebellar degeneration. Cerebellum. 2019;18:245. https://doi.org/10.1007/s12311-018-0987-5.
5. Joubert B, Gobert F, Thomas L, et al. Autoimmune episodic ataxia in patients with anti-CASPR2 antibody-associated encephalitis. Neurol Neuroimmunol Neuroinflamm. 2017;4(4):e371. Published 2017 Jun 14. https://doi.org/10.1212/NXI.0000000000000371
6. Miske R, Gross CC, Scharf M, et al. Neurochondrin is a neuronal target antigen in autoimmune cerebellar degeneration. Neurol Neuroimmunol Neuroinflamm. 2016;4(1):e307. Published 2016 Dec 5. https://doi.org/10.1212/NXI.0000000000000307
7. Mitoma H, Adhikari K, Aeschlimann D, Chattopadhyay P, Hadjivassiliou M, Hampe CS, et al. Consensus paper: neuroimmune mechanisms of cerebellar ataxias. Cerebellum. 2016;15:213–32.
8. Mitoma H, Manto M, Hampe CS. Immune-mediated cerebellar ataxias: from bench to bedside. Cerebellum & Ataxias. 2017;4:16.
9. Mitoma H, Hadjivassiliou M, Honnorat J. Guidelines for treatment of immune-mediated cerebellar ataxias. Cerebellum & Ataxias. 2015;2:14.
10. Wang H, Nong Y, Bazan F, Greengard P, Flajolet M. Norbin: a promising central nervous system regulator. Communicative & Integrative Biology. 2010;3:487–90.
11. Istvanffy R, Weisenhorn DMV, Floss T, Wurst W. Expression of neurochondrin in the developing and adult mouse brain. Dev Genes Evol. 2004;214:206–9.
12. Wang H, Westin L, Nong Y, Birnbaum S, Bendor J, Brismar H, et al. Norbin is an endogenous regulator of metabotropic glutamate receptor 5 signaling. Science. 2009;326:1554–7.
13. Rommel FR, Miske R, Stocker W, Arneth B, Neubauer BA, Hahn A. Chorea minor associated with anti-neurochondrin autoantibodies. Neuropediatrics. 2017;48:482–3.
14. Mitoma H, Manto M, Hampe CS. Time is cerebellum. Cerebellum. 2018;17:387–91.