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Autoimmune Brainstem Encephalitis: A Rare Case with Anti-RhoGTPase-activating Protein 26 Antibody Positive

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Introduction

The antibody against RhoGTPase-activating protein 26 (ARHGAP26) was initially considered as a member of the pathogenic antibodies in subacute autoimmune cerebellar ataxia(ACA) [1]. It is now indicated that this antibody, besides mediating ataxia, is also associated with psychiatric disorders and cognitive impairment [2]. The initial discovery of autoantibodies targeting the RhoGTPase-activating protein 26 (ARHGAP26) occurred in the setting of subacute autoimmune cerebellar ataxia. Subsequent investigations revealed a broader array of clinical manifestations, encompassing psychotic, emotional, and cognitive disturbances. Notably, only a limited number of patients reported thus far have exhibited evidence of a link to tumorous conditions [3]. While the first case of ARHGAP26 antibody-mediated autoimmune cerebellitis in China was reported in 2010 [4]. The reported patient initially manifested with limb ataxia, gait disturbance, dysarthria, and diplopia. Subsequently, two weeks later, the patient gradually exhibited additional symptoms including neuropathic pain, depression, agitation, and anxiety. Furthermore, ARHGAP26 antibodies were detected in the Cerebrospinal Fluid (CSF), accompanied by the presence of positive Oligoclonal Bands (OBs). Brain magnetic resonance imaging (MRI) revealed cerebellar atrophy, and immunotherapy showed limited efficacy. As of now, there have been over 20 reported cases globally related to ARHGAP26 antibodies. About half of these patients have been diagnosed with various types of tumors, including ovarian cancer, breast cancer, melanoma, B-cell lymphoma, prostate adenocarcinoma and gastric adenocarcinoma [5].

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The report describes a rare case of ARHGAP26 antibody-related disease. The characteristics of this case are as follows: an elderly female patient with insidious onset and long duration of illness. And the initial symptoms were dizziness and unsteady gait, followed by slurred speech and limb tremors. Upon admission, physical examination revealed nystagmus in both eyes and cognitive decline. Ultimately, through comprehensive screening of serum and CSF antibodies, the diagnosis was confirmed as anti-ARHGAP26 antibody-related brainstem cerebellitis. Treatment with methylprednisolone pulse therapy, plasma exchange, and continuous immunosuppressive therapy partially reversed the condition, but the effectiveness of the treatment was limited.

Case presentation

The patient, an 82-year-old woman, was admitted to the No. 905 Hospital of PLA Navy on November 9, 2023, for treatment of "dizziness, unsteady walking, slurred speech, and twitching of the limbs for more than a year". The patient presented with dizziness, unsteady walking with nausea and vomiting, no visual rotation, impaired consciousness, profuse sweating, and panic in late March 2022. The brain MRI was preformed in the local hospital suggesting lacunar infarcts with multiple ischemic foci without any special diagnosis or treatment. At the beginning of April 2022, she started to show slurred speech, still had dizziness and unsteady walking, so he went to Nanjing Gulou Hospital to improve the brain MRI enhancement. The results reflected cerebral white matter lesions around the lateral ventricles on both sides, the center of the semiovals and the radiocoronal area. There was no abnormality of the cerebral artery and cerebral vein examination. Lumbar puncture was performed, while pressure was unknown. Other test results included leukocytes 48*10^6/L (lymphocytes 100%), protein 0.53g/L. The presence of Oligoclonal Bands (OCBs) in the cerebrospinal fluid was positive, indicating a possibility of viral encephalitis. In response, antiviral treatment with acyclovir, as well as immunomodulatory therapy consisting of methylprednisolone (40 mg iv qd) and cyclophosphamide (200 mg iv every 1/3 day), was administered. During the course of the disease, cattered petechiae appeared in both lower limbs. Thus, cyclophosphamide was discontinued (cumulative 800 mg) combined with hormone gradual reduction (20 mg po qd) and azathioprine (50 mg po bid). The patient's dizziness symptoms were relieved, while shaking symptoms gradually appeared in the left lower limb, right upper limb. After discharge from the hospital, the dosage of methylprednisolone tablets gradual reduced to 8mg per day orally. After the rehabilitation, the patient's limb shaking symptoms gradually aggravated. In June 2022, she was admitted to a hospital in Nanjing, and her blood test showed that autoantibody RO52 antibody (+++) and anti-mitochondrial antibody type 2 (+). Brain MRI showed multiple ischemic lesions in the left frontal lobe and bilateral centrum semiovale. The condition of CSF included pressure 90 mmH20, white blood cell 6*10^6/L (lymphocyte 100%), protein 0.53 g/L, glucose 3.3 mmo1/L, chloride 121 mmo1/L . And IgG levels increased to 43.80 mg/L. In blood and CSF, the results showed that paraneoplastic antibody was negative, autoimmune encephalitis antibody was negative, OCB was positive, anti-Myelin Oligodendrocyte Glycoprotein (MOG) antibody IgG antibody 1:10 (+). Autoimmune encephalitis was considered, and methylprednisolone (500 mg qd*3d+240 mg qd*3d+120 mg qd*3d) was given. After discharge, the patient was treated with methylprednisolone tablets (48 mg qd) and azathioprine (100 mg qd), and the symptoms did not recover significantly. In late July 2022, the patient exhibited cough and sputum with low-grade fever. The examinations were improved in a hospital in Nanjing, and community-acquired pneumonia was considered. Due to a pneumonia episode, the use of AZA was suspended. Soon afterwards, steroid therapy was rapidly reduced to withdrawal, anti-infection and symptomatic treatment were given. The patient's pneumonia improved, but the symptoms of limb tremor, vague speech, and walking instability remained. The past history was unremarkable.

Physical examination on admission showed clear consciousness, slurred speech, dysarthsia, uncooperative response, impaired memory and calculation, MMSE score 22 (primary school education), binocular gaze to the left, horizontal to the left nystagmus, bilateral frontal wrinkles symmetry, shallow left nasolabial fold, right deviation of mouth Angle, weakened pharyngeal reflex on both sides, suspicious right deviation of tongue extension, and negative cranial nerves. The depth and superficial sensation of both limbs, the muscle strength and tension of the extremities were normal. The tendon reflexes of the extremities were weakened, the bilateral finger, nose, heel and knee tibial tests were unstable, and the right Babinski sign was positive.

Auxiliary examination after admission: Blood test results showed that total cholesterol was 6.2 mmol/L (↑), low-density lipoprotein was 4.33 mmol/L (↑), serum anti-nRNP/Sm antibody and anti-SS-A (52) antibody were weakly positive. In the blood, complement protein 3(C3) was 0.84 g/L (↓, normal range: 0.9-1.8 g/L), transferrin was 1.89 g/L (↓, normal range: 2-3.6 g/L), procalcitonin was 0.56 ng/ml (↑, normal range: 0-0.05 ng/ml), interleukin-6 (IL-6) was 9.4 pg/ml (↑, normal range: 0-7.0 pg/ml). Other blood tests including routine blood tests, erythrocyte sedimentation rate, liver and kidney function, electrolytes, tumor markers, thyroid function, blood ammonia, folic acid, vitamins, etc. showed no significant abnormalities. Blood TB cell subpopulation analysis revealed: total T lymphocytes were 73.14% (↑, normal range: 64.5±8.3%), total B lymphocytes were 5.64% (↓, normal range: 9.6±2.6%), memory B cells were 1.44% (↓, normal range: 8.34-54.76%), and naive B cells were 4.20% (↓, normal range: 5.9-13.9%). Blood gas analysis: PH 4.5, PC O2 40 mmHg, PO2 78 mmHg (↓), and glucose 8.2 mmol/L (↑). Lumbar puncture indicated that CSF pressure was 95 mmH2O, red blood cell count was 0×10^6/L, white blood cell count was 15×10^6/L (↑, mainly lymphocytes), protein was 0.48 g/L (↑), chloride and glucose were normal, OCB was type II, bacterial and fungal cultures were negative, and flow cytometry and exfoliated cell examination did not reveal evidence of malignant tumor cells. Antibodies to autoimmune encephalitis, paraneoplastic syndrome, and demyelinating antibodies were negative in blood and CSF. ARHGAP26 antibody was positive in CSF and serum with titers of 1:320 and 1:100 respectively. TBA staining was positive in the cerebellum, hippocampus, and cerebral cortex in CSF (Figure 1). The whole-body PET-CT and gastroscopy showed no evidence of malignancy. Brain MRI plain and enhanced scan revealed multiple old lacunar infarcts in the basal ganglia, corona radiata, frontal lobe, temporal lobe and centrum semiovale on both sides, and atrophy of cerebellum and brain (Figure 2). Cranial [18F] GE-180 tracking new Translocator Protein (TSPO) PET showed no obvious abnormality (Figure 3). No abnormal enhancement lesions were found. Electroencephalogram showed abnormal enhancement of θ and δ band power in both hemispheres.

Combined with the results of auxiliary examination and medical history, the case was diagnosed as autoimmune brain-

stem encephalitis with positive anti-ARHGAP26 antibody. The patient was treated with methylprednisolone pulse therapy (500 mg qd*5d+250 mg qd*3d+120 mg qd*3d), followed by double membrane plasma exchange for 6 times. After that, the patient's dizziness and vague speech improved, but she still had walking instability and limb shaking. After discharge, the patient was sequentially treated with prednisone acetate tablets 55 mg/d orally, and then the dose was reduced by 5 mg every week until the dose was 40 mg/d. One week later, cyclophosphamide (2 g of induction therapy was given first, and then 800 mg once a month) was given.

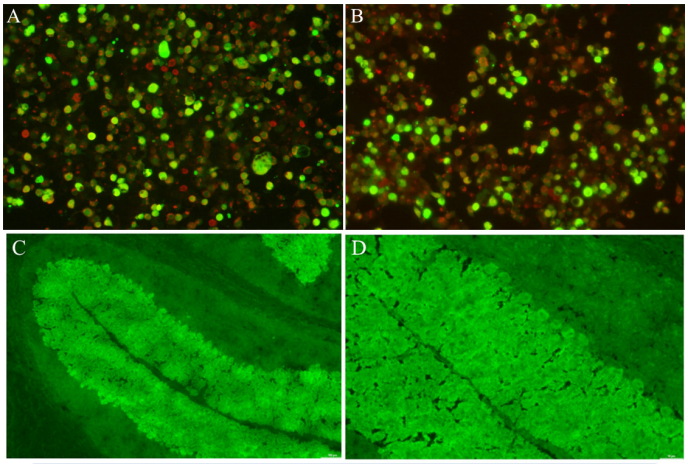

Figure 1: Antibody detection of the patient with anti- RhoGTPase-activating protein 26 antibody positive.
(A) CSF ARHGAP26 antibody IgG positive 1:320+ (CBA method);
(B) Serum ARHGAP26 antibody IgG positive 1:100+ (CBA method).
(C) and **(D)** CSF cerebellar antibody positive.

Discussion

ARHGAP26 antibody, also known as focal adhesion kinase-associated gtpase regulator (GFAR1) -specific immunoglobulin G (IgG) autoantibody, is still rare in related diseases [1]. In more than 20 case reports to date, the ARHGAP26 autoimmune neural spectrum includes cerebellar ataxia, limbic encephalitis, peripheral somatic neuropathy, and autonomic neuropathy (isolated or with cerebellar ataxia) [6-9]. Specific neurological manifestations include: Ataxia (gait, limb), dysarthria, nystagmus, mental and behavioral disorders, dizziness, cognitive impairment, depression, hyperactivity, tremor, gastroparesis, long tract signs, pseudobulbar affect, large and small fiber neuropathy [6-8]. The patient presented cerebellar symptoms of limb ataxia, dizziness and binocular horizontal nystagmus, accompanied by left central facial paralysis, right-sided positive pathological reflexes and dysarthria as the main symptoms of brainstem involvement. In addition, the patient had involuntary limb jitter during the course of the disease, suggesting that the extrapyramidal system was damaged.

In the current detection, ARHGAP26 is rare as a member of the ACA (autoimmune cerebellar) antibody panel [7]. ACA is a cerebellar syndrome mediated by autoimmune mechanisms. Antibodies that are pathogenic or diagnostically-specific can be detected in the serum or CSF of patients, including anti-neuronal nuclear antibody type 1 (anti-Hu), Purkinje cytoplasmic antibody type 1 (anti-Yo), anti-neuronal nuclear autoantibody 2 (anti-Ri), Purkinje cell antibody (Tr/DNER), anti-glutamate decarboxylase (GAD) [10-12]. Compared with other common ACA antibodies, the detection rate of ARHGAP26 antibody is still low. Due to the complex composition of serum, the result of positive CSF but negative serum may occur when the titer is low.

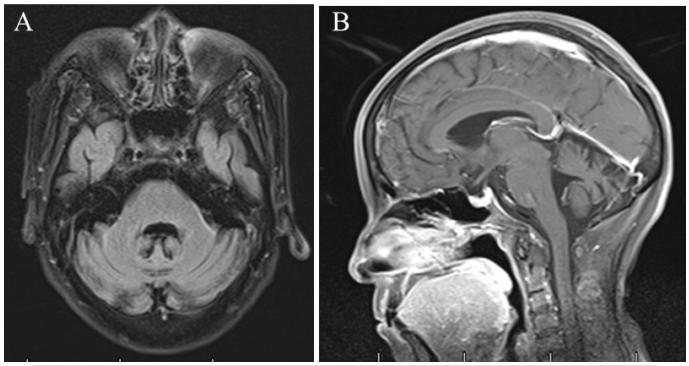

Figure 2: Brain MRI of the patient with anti- RhoGTPase-activating protein 26 antibody positive. Cerebellar atrophy was seen both **(A)** and **(B)** on magnetic resonance examination.

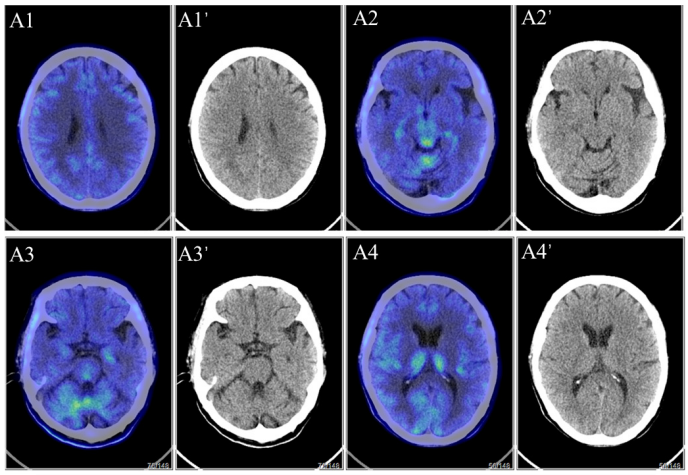

Figure 3: Cranial TSPO-PET of the patient with anti- RhoGTPase-activating protein 26 antibody positive. No obvious TSPO distribution was observed in the cerebral cortex and midbrain region in the TSPO-PET examination.

And because the detection method is different, sometimes the antibody titer and positive rate will be biased [13]. Therefore, in order to improve the positive rate of antibody detection and reduce the possibility of missed diagnosis, it is recommended that serum and CSF be sent together for antibody detection in clinical practice, and different detection methods (such as TBA) can be used for verification if necessary. The patient's CSF and serum were tested at the same time for ACA antibody, paraneoplastic syndrome antibody, OB, and central nervous system demyelinating disease autoantibody. The results showed that ARHGAP26 antibody was positive in both CSF and serum with a respective titer of 1:320 and 1:100. Meanwhile, TBA staining was positive in the cerebellum, hippocampus and cerebral cortex, which supported the existence of ARHGAP26 antibody and its potential pathogenicity.

Anti- ARHGAP26 antibodies not only have dramatic effects on the nervous system, but also have a direct link to the emergence of underlying tumors. The appearance of anti-ARHGAP26 antibodies is thought to be the product of an immune response that may be triggered by the underlying tumor. About 40% of patients with anti-ARHGAP26 antibodies are found to have occult tumors, including ovarian cancer, breast cancer, melanoma, B-cell lymphoma, prostate adenocarcinoma and gastric adenocarcinoma [14]. In some cases, tumor removal or specific tumor therapies have resulted in marked neurologic improvement, which further emphasizes the concept of paraneoplastic syndromes, in which underlying tumors may trigger or exacerbate

neurologic disorders through immune-mediated mechanisms [5]. It is difficult to screen for potential tumors according to the same criteria, which partly affects the accuracy of tumor detection rate. The importance of systematic tumor screening in patients with anti-ARHGAP26 antibody-associated encephalitis remains to be affirmed [15]. It can not only improve the understanding of paraneoplastic syndromes, but also optimize the treatment plan and improve the prognosis of patients. In this case, there were no obvious abnormalities in the serum tumor markers, and the whole-body PET-CT and gastrointestinal endoscopy showed no evidence of malignancy. However, the patient's breast ultrasound report showed that there was a solid nodule with calcification in the right breast (BI-RADS 3-4a), and she still needed to be closely followed up to provide clinical data for further understanding of the relationship between the antibody and the tumor.

At present, it is believed that in the early stage of ARHGAP26 antigen-related disease, MRI is normal in most cases, but cerebellar atrophy, brainstem atrophy or brain atrophy can be found in the later stage [16]. In addition, PET-CT can show cerebellar hypermetabolism in the early stage of the disease, and cerebellar atrophy and hypometabolism may occur with the progression of the disease. The patient visited our hospital at the 19th month of the disease course and was found to have multiple lacunar infarcts on brain MRI, accompanied by cerebellar atrophy and mild brain atrophy. TSPO-PET showed no obvious abnormality in the patient.

In the CSF analysis of ARHGAP26 antibody-associated diseases, most cases may show hypercellularity or normal CSF, and some may be positive for Oligoclonal bands (OCBs) [17]. These findings, including lymphocytic inflammation and positive OCBs, observed in the CSF at 1, 3, and 19 months of the disease course, confirmed the autoimmune pathogenic factor of the disease. The production of ARHGAP26 antibody has not been characterized. Among the hypotheses of antibody formation, on the one hand, the antibody can be induced by infection, which leads to the exposure of autoantigens and the production of anti-neuronal antibodies [18]. On the other hand, it can also be triggered by other autoimmune diseases such as Hashimoto's thyroiditis and Sjogren's syndrome [4]. The patient's serum and CSF were negative for autoimmune encephalitis antibodies, paraneoplastic antibodies, anti-AQP4, and anti-GFAP antibodies 3 months after onset. The serum anti-Myelin Oligodendrocyte Glycoprotein (MOG) IgG antibody was 1:10 (the antibody titer was low, and it was considered non-pathogenic). In the autoimmune antibodies, anti-Ro52 antibody and anti-mitochondrial antibody were strongly positive, and intracranial infection and pulmonary infection occurred in the course of the disease. It is speculated that both autoimmune diseases and infection may contribute to the subsequent production of ARHGAP26 antibody, though further cases are required to validate this hypothesis. Regarding the pathogenic mechanism of ARHGAP26 antibody, current studies have suggested that T cell-mediated immunity to the target antigen of ARHGAP26 antibody plays an important role in the disease [19]. In this case, the blood T cell subset analysis showed that the total T cells accounted for 73.14%, total B cells 5.64%, memory B cells 1.44%, and naive B cells 4.20%. It supports the idea that T cell-mediated immune mechanisms play a role in the disease. In addition, the patient's thyroid function antibody was negative, and the anti-NRNP / Sm antibody and anti-SS-A (52) antibody were weakly positive in autoimmune antibodies testing. The results of the tear film break-up time test were normal, excluding Sjogren's syndrome and other connective tissue diseases. While the role of anti-NRNP /Sm antibody and anti-SS-A (52) antibody in this disease still needs to be further confirmed.

As with other ACA pathogenic antibodies, the final common pathological outcome of cerebellar lesions caused by ARHGAP26 antibody is irreversible loss of Purkinje cells. However, some scholars have used physiological methods to monitor the survival indicators of cerebellar function, indicating that this kind of disease has the characteristics of reversibility and treatability in the early stage, and also indicating the importance of early diagnosis and treatment [1]. Other scholars believe that the efficacy in some patients with the disease after immunotherapy (such as IVIG, IVMP, RTX.) is not obvious, pointing out that immunotherapy did not reverse neurological dysfunction., Eventually, these patients' conditions stabilize, but they remain wheelchair dependent, and their quality of life is reduced [2-4]. In this case, the symptoms of the patient were partially improved after steroid pulse therapy and plasmapheresis followed by oral steroids and immunosuppressive therapy, however, the symptoms were still worse than normal, suggesting that ARHGAP26 antibody could cause permanent loss of some Purkinje cells and the symptoms were irreversible. The progression of the disease will be closely followed to provide clinical information on whether early initiation of treatment may reduce neurological dysfunction.

Conclusion

ARHGAP26 antibody-related encephalopathy is still rare, and more clinical data need to be accumulated. For patients with gait instability, dizziness, and dysarthria as the main symptoms, we should actively screen for ARHGAP26 antibody and other ACA-related antibodies, and pay attention to the presence of infection, other autoimmune antibodies and tumors, so as to find the cause as early as possible, achieve early diagnosis and treatment, and avoid permanent neurological dysfunction.

Author declarations

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Ethics approval and consent to participate

Written informed consent was obtained from the patient and the aims of the study completely explained.

Conflict of interest

All authors have no conflicts of interest to report.

References

1. Wallwitz U, Brock S, Schunck A, Wildemann B, Jarius S, Hoffmann FJ Jon. From dizziness to severe ataxia and dysarthria: New cases of anti-Ca/ARHGAP26 autoantibody-associated cerebellar ataxia suggest a broad clinical spectrum. 2017; 309: 77-81.

2. Bartels F, Prüss H, Finke CJ Fin. Anti-ARHGAP26 Autoantibodies Are Associated with Isolated Cognitive Impairment. 2018; 9:656.

3. Bartels F, Prüss H, Finke C. Anti-ARHGAP26 Autoantibodies Are Associated with Isolated Cognitive Impairment. Frontiers in neu-

rology. 2018; 9: 656.

4. Sven J, Klaus P W, Sigrun H, Heike H, Brigitte WJJN. A new Purkinje cell antibody (anti-Ca) associated with subacute cerebellar ataxia: immunological characterization. 2010; 7.

5. Jarius S, Wildemann BJJon. '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. 2015; 12: 167.

6. Sven J, Pedro M-G, Adelaida León H, Jan Christoph B, Kathrin B, Jens Ulrich R, et al. Two new cases of anti-Ca (anti-ARHGAP26/GRAF) autoantibody-associated cerebellar ataxia. 2013; 10.

7. Sarah D, Astrid N, Annerose Z, Eberhard S, Kathrin B, Winfried S, et al. Anti-Ca/anti-ARHGAP26 antibodies associated with cerebellar atrophy and cognitive decline. 2014; 267.

8. Ulrike W, Sebastian B, Antje S, Brigitte W, Sven J, Frank HJJN. From dizziness to severe ataxia and dysarthria: New cases of anti-Ca/ARHGAP26 autoantibody-associated cerebellar ataxia suggest a broad clinical spectrum. 2017; 309.

9. S J, B W, W S, A M, K P WJJN. Psychotic syndrome associated with anti-Ca/ARHGAP26 and voltage-gated potassium channel antibodies. 2015; 286.

10. Jiajie C, Lingchun L, Hongyan Z, Jinming H, Rong L, Xiarong G, et al. Autoimmune nodopathy with anti-contactin 1 antibody characterized by cerebellar dysarthria: a case report and literature review. 2024; 15.

11. Albert S, Francesc GJCON. Neuronal antibodies in nonparaneoplastic autoimmune cerebellar ataxias. 2024; 37.

12. Mario M, Hiroshi MJBS. Recent Advances in Immune-Mediated Cerebellar Ataxias: Pathogenesis, Diagnostic Approaches, Therapies, and Future Challenges-Editorial. 2023; 13.

13. Mange L, Haitao R, Lei W, Siyuan F, Lin B, Hongzhi GJJN. Prognostic and relapsing factors of primary autoimmune cerebellar ataxia: a prospective cohort study. 2023; 271.

14. Jarius S, Wildemann BJ Jon. '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. 2015; 12: 168.

15. Jarius S, Martínez-García P, Hernandez A, Brase J, Borowski K, Regula J, et al. Two new cases of anti-Ca (anti-ARHGAP26/GRAF) autoantibody-associated cerebellar ataxia. 2013; 10: 7.

16. Doss S, Nümann A, Ziegler A, Siebert E, Borowski K, Stöcker W, et al. Anti-Ca/anti-ARHGAP26 antibodies associated with cerebellar atrophy and cognitive decline. 2014; 267: 102-4.

17. Du X, Qian X, Papageorge A, Schetter A, Vass W, Liu X, et al. Functional interaction of tumor suppressor DLC1 and caveolin-1 in cancer cells. 2012; 72: 4405-16.

18. A F, M V-G, J HJRN. Neurological adverse events of immune checkpoint inhibitors: An update of clinical presentations, diagnosis, and management. 2023; 179.

19. Jarius S, Metz I, König F, Ruprecht K, Reindl M, Paul F, et al. Screening for MOG-IgG and 27 other anti-glial and anti-neuronal autoantibodies in 'pattern II multiple sclerosis' and brain biopsy findings in a MOG-IgG-positive case. 2016; 22: 1541-9.