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CASE REPORT

Anti-glial fibrillary acidic protein antibody and anti-aquaporin-4 antibody double-positive neuromyelitis optica spectrum disorder: A case report

Ting-Yu Jin, Bing-Tong Lin, Li-Jv Dai, Xia Lu, Han Gao, Jin Hu

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Abstract

BACKGROUND

A case of neuromyelitis optica spectrum disorder (NMOSD) with positive cerebrospinal fluid (CSF) anti-aquaporin-4 antibody (AQP4-IgG) and anti-glial fibrillary acidic protein IgG (GFAP-IgG) at the time of relapse was reported. The exact roles of GFAP-IgG in NMOSD are not fully understood and are the subject of ongoing research. This study revealed the possible connection between GFAP-IgG and the occurrence or development of diseases.

CASE SUMMARY

A 19-year-old woman was admitted to the hospital due to a constellation of symptoms, including dizziness, nausea, and vomiting that commenced 1 year prior, reoccurred 2 mo ago, and were accompanied by visual blurring that also began 2 mo ago. Additionally, she presented with slurred speech and ptosis, both of which emerged 1 mo ago. Notably, her symptoms deteriorated 10 d prior to admission, leading to the onset of arm and leg weakness. During hospitalization, magnetic resonance imaging showed high T2-fluid attenuated inversion recovery signals, and slightly high and equal diffusion-weighted imaging signals. The serum antibody of AQP4-IgG tested positive at a dilution of 1:100. CSF antibody testing showed positive results for GFAP-IgG at a dilution of 1:10 and AQP4-IgG at a dilution of 1:32. Based on these findings, the patient was diagnosed with NMOSD. She received intravenous methylprednisolone at a daily dose of 500 mg for 5 d, followed by a tapering-off period. Afterward, the rate of reduction was gradually slowed down and the timely use of immunosuppressants was implemented.

CONCLUSION

The CFS was slightly GFAP-IgG-positive during the relapse period, which can aid in the diagnosis and treatment of the disease.

Key Words: Anti-glial fibrillary acidic protein antibody; Neuromyelitis optica spectrum disorder; Anti-aquaporin-4 antibody; Cerebrospinal fluid; Case report

Core Tip: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disorder that affects the central nervous system. Here, a case of NMOSD with positive cerebrospinal fluid aquaporin-4 antibody and anti-glial fibrillary acidic protein antibody (GFAP-IgG) at the time of the relapse was reported. The exact role of GFAP-IgG in NMOSD remains a subject of debate and research, with some studies suggesting it is pathogenic and plays a role in disease development or progression. This case reveals the potential role of GFAP-IgG in NMOSD. The findings suggest a possible association between GFAP-IgG and the initiation or advancement of the disease.

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INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disorder affecting the central nervous system (CNS), specifically the optic nerves and spinal cord. It is characterized by immune-mediated inflammation and demyelination of the affected tissues, classified as a humoral immune spectrum disease. In 2005, Lennon *et al*[1] discovered anti-neuromyelitisopica antibody in the serum of NMOSD patients, which was later confirmed to target anti-aquaporin-4 antibody (AQP4-IgG). This finding became one of the primary diagnostic criteria for NMOSD. The main diagnostic basis of NMOSD includes six core symptoms: optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, acute diencephalic clinical syndrome, and symptomatic cerebral syndrome[2]. Glial fibrillary acidic protein (GFAP) serves as the main intermediate filament of the astrocyte skeleton[3]. Increased levels of GFAP in the cerebrospinal fluid (CSF) of NMOSD patients indicate astrocyte injury and are considered a biomarker[4]. Notably, elevated CSF-GFAP levels in patients with multiple sclerosis (MS) are associated with higher disability and worsening disability, particularly in late-stage patients[5]. It is indicated that CSF-GFAP partially reflects reactive astrogliosis[6].

Anti-GFAP antibodies (GFAP-IgG) refer to antibodies that are directed against GFAP and have been observed in the blood and CSF of patients with autoimmune diseases such as neuromyelitisopica, NMOSD, encephalitis, and other neurological disorders, suggesting an immune attack against astrocytes, leading to CNS inflammation and damage. While the detection of GFAP-IgG has been used as a diagnostic tool, its specificity and sensitivity require further research [7]. Zhang *et al*[8] reported a case of an NMOSD patient who tested negative for AQP4-IgG but positive for GFAP-IgG in 2020. In this report, we present a case of an NMOSD patient with positive AQP4-IgG and GFAP-IgG in the CSF during a relapse.

CASE PRESENTATION

Chief complaints

A 19-year-old woman was admitted to the hospital due to a constellation of symptoms, including dizziness, nausea, and vomiting that commenced 1 year prior, reoccurred 2 mo ago, and were accompanied by visual blurring that also began 2 mo ago. Additionally, she presented with slurred speech and ptosis, both of which emerged 1 mo ago. Notably, her symptoms deteriorated 10 d prior to admission, leading to the onset of arm and leg weakness.

History of present illness

One year ago, the patient experienced dizziness, nausea, and vomiting, leading her to seek examination by a gastroenterologist at a nearby hospital. Gastrointestinal endoscopy was performed and revealed no significant abnormalities. Her symptoms were completely alleviated with proton pump inhibitor treatment.

Two months prior to admission, she had a recurrence of dizziness, nausea, vomiting, and mild visual blurring. She was re-examined by the gastroenterology department, where another endoscopic examination showed no obvious abnormalities. Additionally, she visited the ophthalmology clinic for an eye exam and visual acuity test, which revealed nearsightedness in both eyes, with a naked eye visual acuity of 0.4 in her left eye and 0.6 in her right eye, and a corrected visual acuity of 1.0 in both eyes. No evident abnormalities were found in her eye fundus. Her symptoms slightly improved after receiving antacid and antiemetic medication, leading to her discharge from the hospital.

One month prior to admission, her symptoms worsened, characterized by increased dizziness, nausea, vomiting, and visual blurring, as well as the development of slurred speech and drooping eyelids. She was subsequently admitted to the local hospital's neurology department. The patient had previously sought medical attention at a local grass-roots hospital, where her magnetic resonance imaging (MRI) was reviewed and revealed new findings. It is worth noting that the limited expertise of radiologists at such hospitals may contribute to potential inaccuracies in the diagnosis. Her brain MRI report initially indicated no obvious abnormalities, but upon further review, the MRI showed abnormal T1-weighted imaging (T1WI) signals (Figure 1A-D), high T2-fluid attenuated inversion recovery (T2-FLAIR) signals (Figure 1E-H), slightly high and equal diffusion-weighted imaging (DWI) signals (Figure 2A-D), and normal apparent diffusion coefficient (ADC) values (Figure 2E-H).

Ten days prior to admission, her symptoms worsened further, and she developed weakness in her arms and legs. As a result, she was transferred to our hospital's neurology department.

History of past illness

The patient had no previous history of similar conditions.

Personal and family history

The patient denied any family history of similar conditions.

Physical examination

A neurological examination revealed both vertical and horizontal nystagmus, slurred speech, drooping eyelids, and muscle strength of grade 4 in the bilateral lower extremities according to the muscle strength grading scale (maximum score 5); her Expanded Disability Status Scale (EDSS) score was 7 points. She had hyperactive reflexes in the biceps, triceps, knees, and Achilles tendons, and positive bilateral Babinski's sign.

Laboratory examinations

Laboratory tests for various antibodies were performed, including serum anti-nuclear antibodies, anti-double-stranded DNA antibodies, anti-neutrophil cytoplasmic antibodies, anti-cardiolipin antibodies, anti-myelin oligodendrocyte glycoprotein antibody (MOG-IgG), anti-myelin basic protein antibody (MBP-IgG), GFAP-IgG, and anti-autoimmune encephalitis antibodies, all of which yielded negative results. However, the serum antibody of AQP4-IgG tested positive at a dilution of 1:100. Lumbar puncture revealed an opening pressure of 115 mm water, with normal levels of CSF protein, glucose, and leukocyte count, and undetectable oligoclonal bands. CSF antibody testing showed positive results for GFAP-IgG at a dilution of 1:10 and AQP4-IgG at a dilution of 1:32, while CSF MBP-IgG, MOG-IgG, and autoimmune encephalitis antibodies were negative. The antibody detection test employed a transfected cell assay, which was further confirmed by the normality of the negative control from the same period.

Imaging examinations

The patient had previously sought medical attention at a local grass-roots hospital, where her MRI was reviewed and revealed new findings. It is worth noting that the limited expertise of radiologists at such hospitals may contribute to potential inaccuracies in the diagnosis. Her brain MRI report initially indicated no obvious abnormalities, but upon further review, the MRI showed abnormal T1WI signals (Figure 1A-D), high T2-FLAIR signals (Figure 1E-H), slightly high and equal DWI signals (Figure 2A-D), and normal ADC values (Figure 2E-H).

One month after the patient's initial MRI scan, a follow-up scan was performed, which showed low signal intensity on T1WI (Figure 3A-D), high signal intensity on T2-FLAIR (Figure 3E-H), slightly high and equal signal intensity on DWI (Figure 4A-D), and normal ADC values (Figure 4E-H) in the medulla oblongata. The location of the abnormal signals remained consistent with the first scan but showed a reduced range and decreased high signal intensity on T2-FLAIR. Additionally, a spinal MRI was conducted, yielding normal results.

FINAL DIAGNOSIS

Based on these findings, the patient was diagnosed with NMOSD.

TREATMENT

She received intravenous methylprednisolone at a daily dose of 500 mg for 5 d, followed by a tapering-off period. During treatment, her limb weakness, vision blurriness, dizziness, slurred speech, and blepharoptosis went into remission. After 2 wk of treatment, her EDSS score decreased to 5 points. Upon discharge, she was prescribed oral prednisone at a daily dose of 60 mg. The dose was gradually decreased from 10 mg to 30 mg daily over the course of each subsequent week. Afterward, the rate of reduction was gradually slowed down and timely use of immunosuppressants.

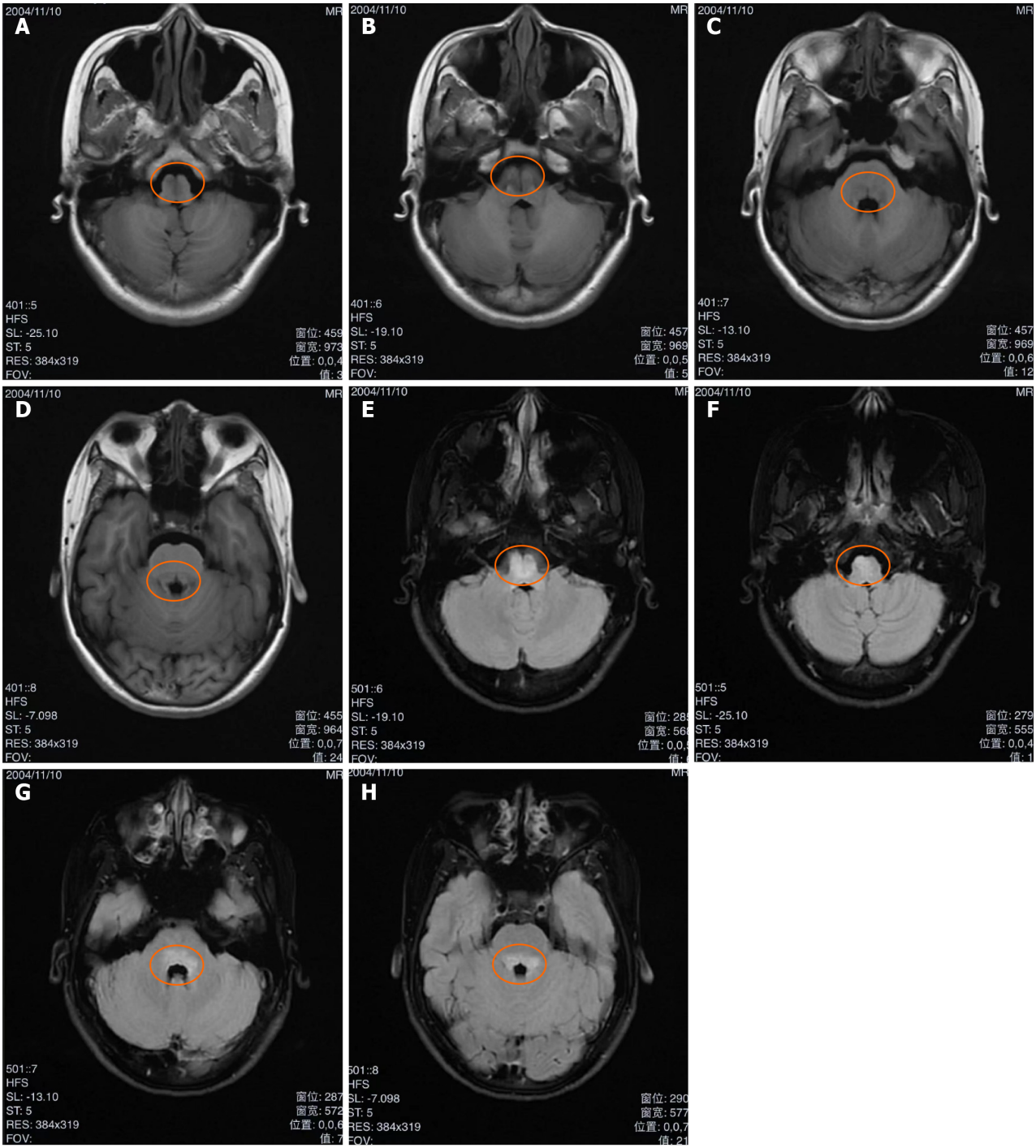

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Figure 1 Patient's first brain magnetic resonance imaging. A-D: Four slices of T1-weighted imaging showing low signals in the medulla oblongata; E-H: Four slices of T2-fluid attenuated inversion recovery showing high signals in the medulla oblongata.

OUTCOME AND FOLLOW-UP

Based on their expertise in NMOSD treatment, we plan to maintain her on corticosteroids for a minimum duration of 6 mo, with follow-up appointments scheduled every 1 to 2 mo. Through August 2023, the patient's condition did not recur and her EDSS score increased to 1 point.

DISCUSSION

The demand for predictive and disease-active biomarkers in NMOSD patients has been widely recognized, leading to an increase in biomarker studies. Among the potential biomarkers investigated, GFAP, an astrocyte protein, appears to be

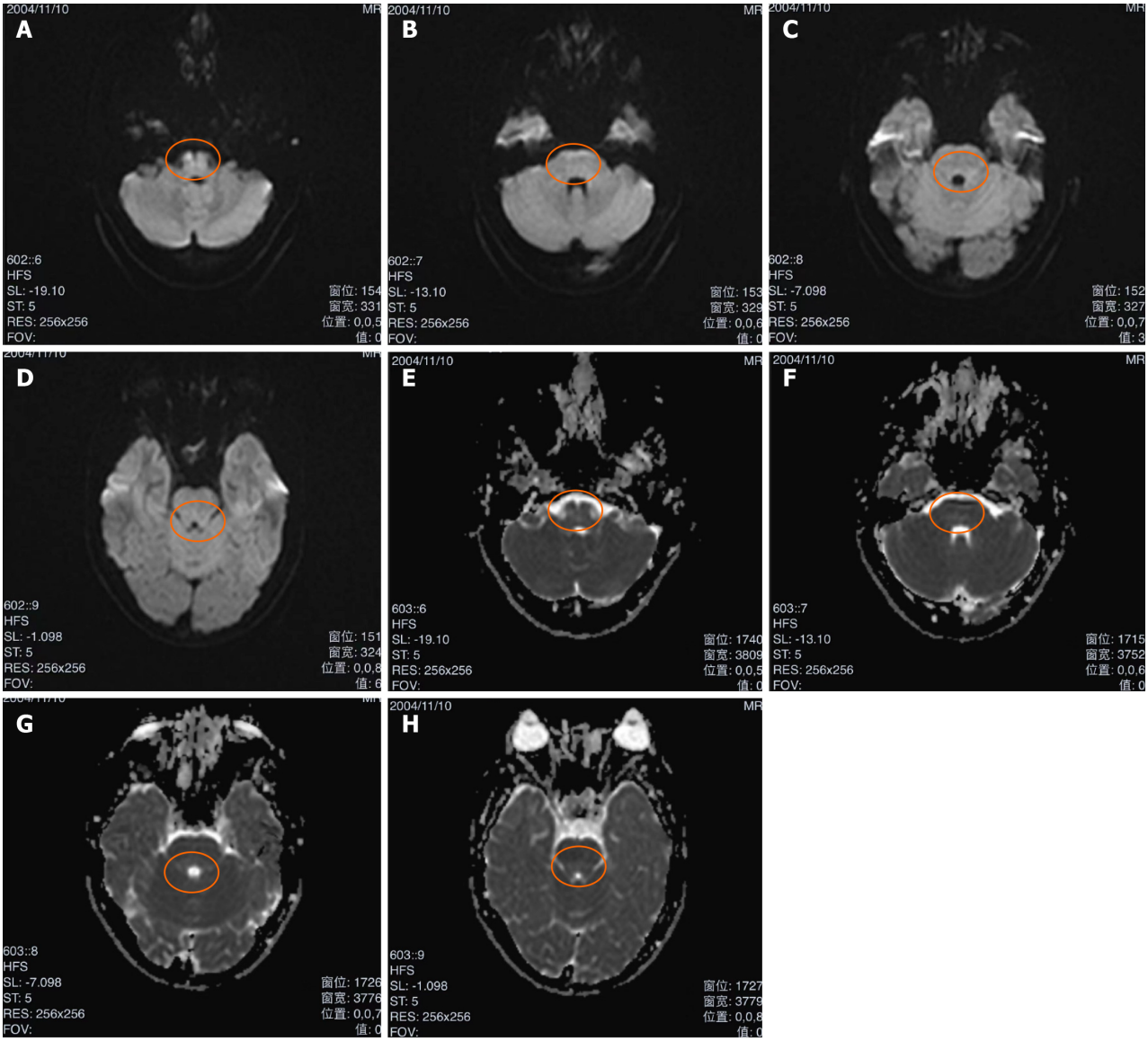

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Figure 2 Patient's first brain magnetic resonance imaging. A-D: Four slices of diffusion-weighted imaging showing slightly high and equal signals in the medulla oblongata; E-H: Four slices of apparent diffusion coefficient showing normal value in the medulla oblongata.

one of the most promising alternatives. In healthy astrocytes, GFAP is expressed moderately, but it is significantly upregulated during brain injury. This increase indicates reactive astrocyte proliferation[9]. Reactive astrocyte hyperplasia is a process caused by various types of brain injury, such as traumatic, metabolic, and inflammatory injury. Transient or permanent morphological and functional changes in astrocytes can result in the formation of glial scars[10].

Current evidence shows that the concentration of GFAP in the CSF and blood of NMOSD patients during an acute attack is higher compared to healthy individuals and patients with MS. In NMOSD, CSF and blood GFAP concentrations increase at the onset, decrease with immunotherapy, and are associated with disability. Furthermore, serum GFAP concentrations in clinically stable NMOSD patients can predict future seizures[10]. Importantly, there is growing evidence to support the predictive value of blood GFAP concentrations for present and future disease activity, particularly in AQP4-IgG-positive NMOSD. GFAP elevation in NMOSD can be explained by lysis of astrocytes and subsequent astrogliosis. Thus, GFAP concentrations in the blood of AQP4-IgG-positive NMOSD patients during clinical remission may reflect ongoing subclinical disease activity, potentially increasing the risk of further attacks[11].

However, the exact roles of GFAP-IgG in NMOSD are still not fully understood and are the subject of ongoing research. It is suggested that these antibodies may be involved in the onset or progression of the disease, but this has yet to be established conclusively. Some studies have proposed that GFAP-IgG can serve as biomarkers for diagnosing NMOSD and distinguishing it from other similar conditions. Others suggest that these antibodies may target and damage specific cells in the CNS, contributing to the disease's pathogenesis[12].

The exact role of GFAP-IgG in NMOSD remains a topic of debate and ongoing research. Some studies argue that they are epiphenomenal and do not directly contribute to the disease, while others suggest their pathogenic involvement in its development or progression[13].

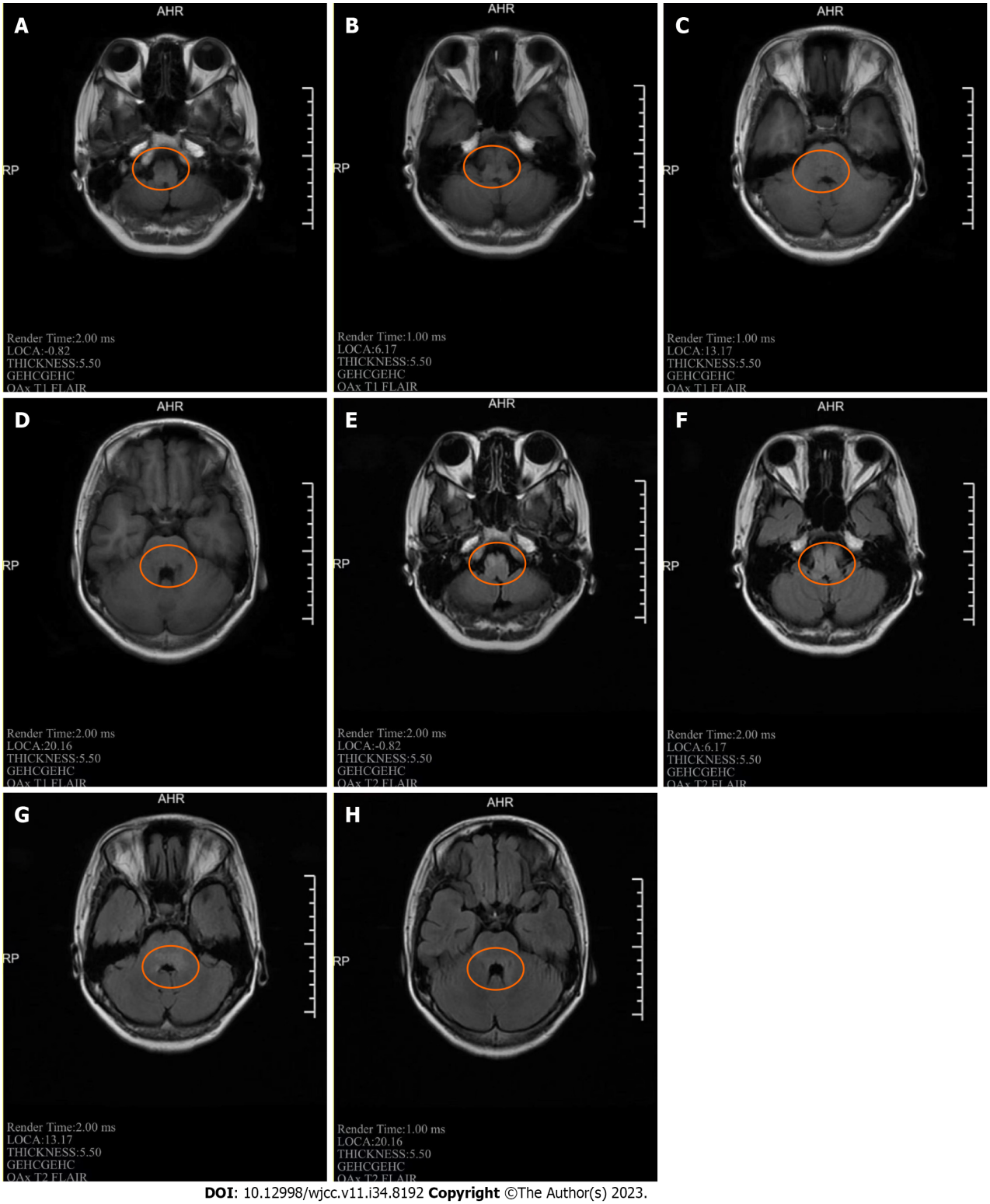

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Figure 3 Patient's second brain magnetic resonance imaging. A-D: Low signal intensity on four slices of T1-weighted imaging in the medulla oblongata; E-H: High signal intensity on four slices of T2-fluid attenuated inversion recovery in the medulla oblongata.

CONCLUSION

The disease described in this study exhibited a pattern of remission and relapse. Notably, during the relapse period, the CSF showed slight positivity for GFAP-IgG. This finding can be valuable in the diagnosis and treatment of the disease.

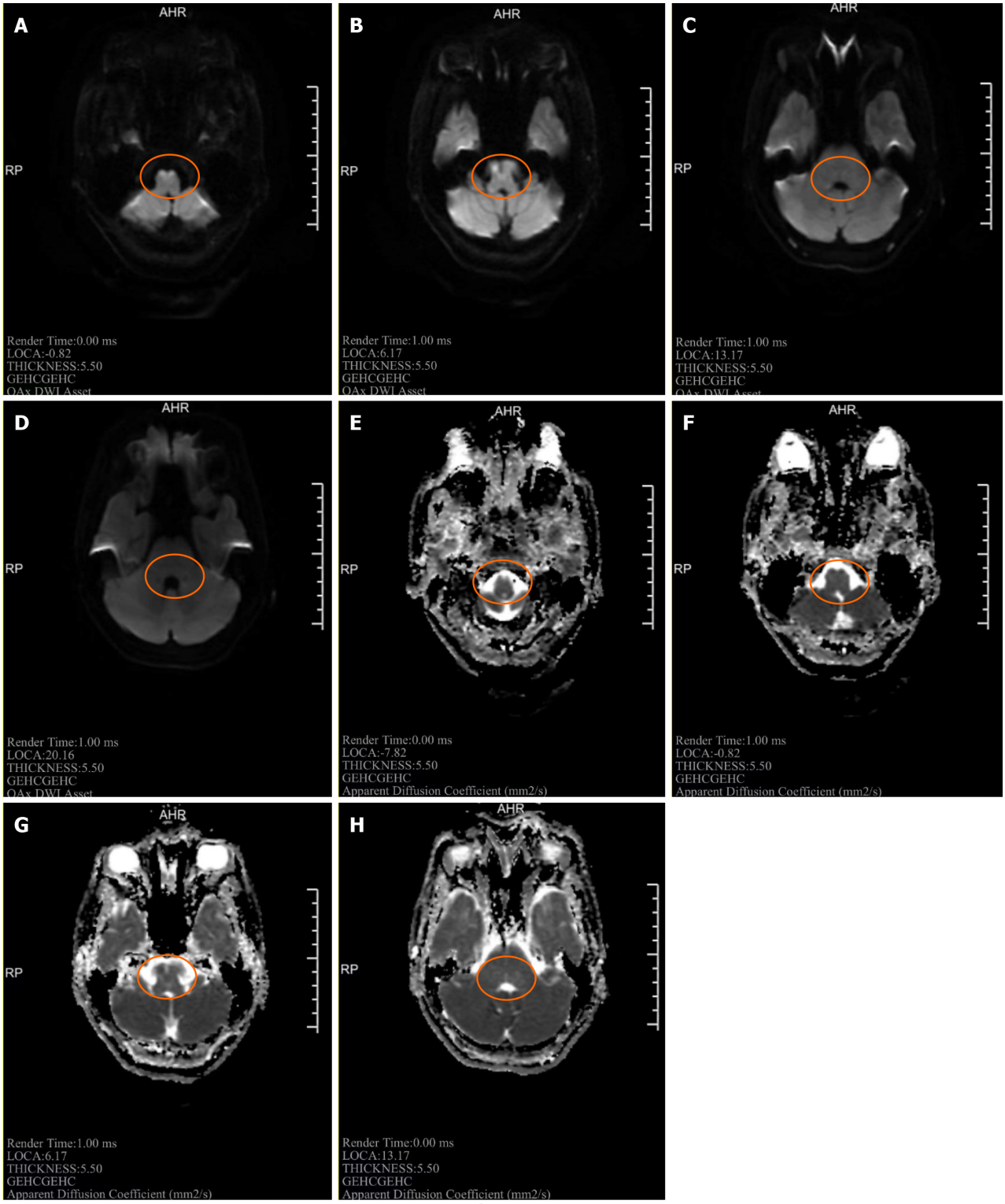

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Figure 4 Patient's second brain magnetic resonance imaging. A-D: Slightly high and equal signal intensity on four slices of diffusion-weighted imaging in the medulla oblongata; E-H: Four slices of apparent diffusion coefficient showing normal value in the medulla oblongata.

FOOTNOTES

Author contributions: Jin TY and Hu J contributed to manuscript writing and editing, and data collection; Lin BT, Dai LJ, Lu X, and Gao H contributed to data collection; Lin BT contributed to conceptualization and supervision; All authors have read and approved the final manuscript.

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