

Clinical Analysis of NMOSD with Area Postrema Syndrome as Initial Symptom

Ting Liu

The First Affiliated Hospital of Hainan Medical University

Lijuan Li

The First Affiliated Hospital of Hainan Medical University

BinJi Liang

Jiamusi University

Xian Li

The First Affiliated Hospital of Hainan Medical University

Lin Ma (✉ 13976921939@163.com)

The First Affiliated Hospital of Hainan Medical University

Research Article

Keywords: Neuromyelitis optica spectrum disorders, area postrema syndrome, magnetic resonance imaging, biomarkers

Posted Date: December 6th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1135084/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at European Journal of Medical Research on December 29th, 2022. See the published version at <https://doi.org/10.1186/s40001-022-00949-9>.

Abstract

Objective: Patients with neuromyelitis optica spectrum disease (NMOSD) with the initial manifestation of area postrema syndrome (APS) often have unexplained nausea and vomiting and are easily misdiagnosed for the NMOSD. The purpose of this study was to report and discuss clinical analysis, including diagnosis and treatment of 4 cases of NMOSD with APS as the first symptom.

Methods: Four patients with intractable nausea and vomiting were selected for the analysis and finally the cases were confirmed for the NMOSD. All of these patients started with misdiagnosis and mismanagement initially.

Results: Among the 4 patients included in this study, 3 were admitted to the department of gastroenterology at the onset of the disease, and 2 of them were not correctly diagnosed and treated on time due to misdiagnosis. Therefore, their symptoms worsened, and they needed to be transferred to ICU for life support. No obvious early medulla lesions were found in one patient. One patient was treated with intravenous immunoglobulin, methylprednisolone, and plasma exchange but there was no significant clinical improvement, and then the disease was relapsed during the treatment with low-dose rituximab.

Conclusion: The clinical manifestations of NMOSD are complex and diverse, and the initial symptoms, onset age of the patient, and MRI findings can all influence the clinicians' judgment of the disease. Early identification of the APS and timely therapy can prevent visual and physical disabilities, even respiratory failure and cardiac arrest. Therefore, it is necessary to identify specific and sensitive serum and imaging markers for predicting the prognosis and recurrence of the disease.

1 Introduction

Neuromyelitis optic spectrum disease(NMOSD) is an immune-mediated inflammatory demyelinating disease of the central nervous system. The typical clinical manifestations are mainly Optic neuritis(ON) and Longitudinally extensive transverse myelitis(LETM). Area postrema syndrome(APS) is relatively rare among the clinical symptoms of NMOSD, and is often presented as nausea and vomiting of unknown cause, which is easy to be misdiagnosed clinically. We retrospectively analyzed the clinical data of 4 patients with NMOSD with the onset of area postrema syndrome, and discussed the pathogenesis, clinical characteristics, diagnosis and treatment of NMOSD, in order to improve clinicians' understanding of this disease and reduce misdiagnosis and mistreatment of patients.

2 Method

2.1 Study population

The current 4 cases are among the 54 patients with AQP4-IgG-positive NMOSD diagnosed in our hospital between 2018 and 2021. We found 5 patients initially presenting with APS, but excluded 1 patient with incomplete medical records. 4 patients included in the study met the 2015 international diagnostic

criteria. These diagnoses were made independently by three experienced neurologists. All 4 patients agreed to the publication of their anonymized clinical data.

2.2 Data collection

We reviewed the patients' medical records, collecting data including demographic, clinical, laboratory, and magnetic resonance imaging (MRI) data, As well as INVH duration, department of first visit, time interval from INVH to the development of core NMOSD syndrome, and other core NMOSD features such as acute diencephalon, acute brainstem, symptomatic brain syndrome, and optic neuritis and acute myelitis.

3 Result

3.1 Case records

Case1 A 31-year-old female patient developed nausea and vomiting of unknown cause more than a month before admission. She was hospitalized in three hospitals, and was diagnosed as "reflux esophagitis and chronic gastritis" by gastroscopy, but the antiemetic treatment was ineffective. Fever and psychiatric symptoms occurred during the period. After taking antipsychotics 4 days before admission, she developed unconsciousness without convulsions, which lasted for more than 10 hours. After waking up, she felt numbness and weakness in limbs, unable to lift, dyspnea, urination and defecation difficulties. After being transferred to ICU of our hospital, MRI plain scan of brain and neck showed multiple abnormal signals in the spinal cord from the medulla oblongata to L1 level, and scattered abnormal signals in bilateral hypothalamus, dorsal pons and medulla oblongata(Fig 1). The serum AQP4-IgG was positive for the first time and was diagnosed as NMOSD. She accepted Intravenous methylprednisolone (IVMP) was treated with Intravenous immunoglobulin (IVIg) after the first dose reduction, followed by 3 plasma exchange. One month after admission, the patient received continuous 4 weeks of low-dose rituximab treatment. Before the end of the treatment course, the patient developed worsening limb weakness, accompanied by nausea, blurred vision and diplopia. Relapse was considered, and IVIg was given to improve the condition and discharge.

Caes 2 A 62-year-old female patient developed nausea, vomiting, numbness and weakness of the right limb, dizziness and headache 1 month ago after catching cold. She went to our hospital 1 day ago and MRI showed abnormal signals in the right thalamus, paraventricular region and left occipital lobe(Fig 1). She was diagnosed as cerebral infarction and discharged after treatment. One month later, the patient came to the hospital again due to dizziness and headache, MRI showed that the original lesion was larger than before, but oligoclonal band were negative, and she was discharged from the hospital. Subsequently, she went to the doctor for 2 times due to recurrent nausea and vomiting. In this time, considering the possible presence of APS, the improved AQP4-IgG test in cerebrospinal fluid was found to be positive and diagnosed as NMOSD. She was discharged after accepted IVMP. She's been taking mycophenolate mofetil out of the hospital ever since.

Case 3 A 23-year-old male presented with intractable nausea and vomiting 1 month ago and was discharged from hospital after treatment for chronic gastritis. One month later, the patient went to the department of Gastroenterology again due to nausea and vomiting. 3 days after admission, nausea and vomiting became worse, accompanied by limb weakness, dizziness, headache and ataxia. MRI of the cervical spine and thoracic spine showed multiple abnormal signal changes in the medulla oblongata, upper cervical medulla (C1-2 vertebral level), and thoracic medulla (T1-2 vertebral level)(Fig 1). The patient was transferred to the Department of Neurology considering neurological diseases. Improved AQP4-IgG test in cerebrospinal fluid was found to be positive and diagnosed as NMOSD. 3 days later, the patient suddenly developed disturbance of consciousness, decreased oxyhemoglobin saturation and decreased blood pressure. He was immediately given oral trachea cannula and breathing machine assisted breathing, and then transferred to ICU for treatment. He was discharged after accepted IVMP and IVIg. Two years later, the patient was admitted with diplopia and brain MRI showed a medulla oblongata lesion extending to the right cerebellum. Consider disease relapse and accept IVMP discharged after treatment.

Case 4 A 30-year-old woman was diagnosed with reflux esophagitis in the department of Gastroenterology at another hospital after repeated vomiting for 2 months. Two months later, the patient was admitted to the neurology department due to numbness and weakness of the right limb. MRI of the cervical spine demonstrates abnormal signals at the medulla oblongata to C2 level(Fig 1). The possibility of central nervous system demyelination disease is considered, the patient was treated with IVMP and discharged. 3 years later, the patient reappeared with weakness, Improved AQP4-IgG test in serum was positive. She was discharged after accepted IVMP. She's been taking mycophenolate mofetil out of the hospital ever since.

3.2 Patient demographics and clinical characteristics

Among the above 4 cases, 3 were female and 1 was male. The onset age ranged from 23 to 62 years, with an average onset age of 36.5 years. All patients developed intractable nausea, vomiting, or hiccups, and these symptoms were excluded from the combination of other systemic diseases. 3 patients had acute myelitis, 2 had optic neuritis and 3 had acute brainstem syndrome, 2 patients had acute diencephalic syndrome and 2 patients had cerebral syndrome. All 4 patients had typical relapses, and 2 of them still had persistent nausea, vomiting, or hiccups.

3.3 Laboratory findings

Patient laboratory test data is summarized in Table 1-2. Serum AQP4-IgG was positive in all 4 patients. Two of the three patients tested for AQP4-IgG in CSF were positive. Recurrent hyponatremia occurred in 2 patients, thyroid peroxidase antibody was elevated in all patients, and rheumatoid factor was positive in 2 patients. In the antinuclear antibody test of 4 patients, 2 patients were positive for anti-SSA antibody and anti-Ro52 antibody. PANCA-IgG antibody were found in 1 patients.

Table 1-Laboratory findings of APS-NMSOD patients.

n	sex	First diagnosis	Duration of INVH (d)	Interval time from APS to OCS (d)	CSF Leucocyte count ($\times 10^6/L$)	TP(mg/L)	Cl(mmol/l)	Lactate dehydrogenase (U/L)	electrolyte disturbance	Other Ab
1	F	reflux esophagitis	25	25	225	975.56	120	64.94	hyponatremia	SSA; Ro52; RA
2	F	cerebral infarction	1238	29	3	287.4	117.5	21	hyponatremia	-
3	M	chronic gastritis	37	834	-	257	116.6	39	-	SSA; Ro52; RA
4	F	reflux esophagitis	65	69	5	433.4	121.2	29	-	PANCA

N: number; Ab: antibody(coexisting);OCS: other core symptoms

3.4 MRI findings

The MRI findings of the 4 patients in the study are summarized in Table 2. MRI of all patients showed abnormal signals of the dorsolateral medulla oblongata, no obvious early medulla lesions in 1 patient, and, 2 patients had medulla oblongata lesions connected to the cervical spinal cord. During follow-up, progression of cerebellar lesions to the medulla oblongata in 1 patient. MRI showed abnormal signals in diencephalon in 2 patients, and abnormal signals in cerebral hemisphere in 2 patients.

Table 2-MRI findings and AQP4-Ab/OB of APS-NMSOD patients.

n	lesion	AQP4-Ab	MOG-Ab	OB
1	MO; Bilateral hypothalamus; VT; DP; C2-T1	+	-	-
2	MO; right thalamus; periventricular; VT; left occipital lobe	+	-	-
3	MO; C1-2; T1-2	+	-	-
3	MO; C1-C2; left occipital lobe	+	-	-

MO: medulla oblongata; VT: ventriculus tertius; DP: dorsal pontine

3.5 Therapy and EDSS score

Table3-therapy and EDSS score before treatment

n	acute attacks	IST	EDSS score before treatment
1	IVMP; PE; IVIg	rituximab	8.0
2	IVMP	mycophenolate mofetil	2.5
3	IVMP; IVIg	-	1.5
4	IVMP	mycophenolate mofetil	2.0

IST: Immunosuppressive therapy; IVMP: Intravenous methylprednisolone; IVIg: Intravenous immunoglobulin; PE: Plasma exchange

4 Discussion

Current epidemiological survey data show that the first onset of NMOSD is mostly in young and middle-aged people, mostly in women, and the incidence of NMOSD is higher in African, Asian and Latin American populations than in white populations. Due to the small sample size and different AQP4 antibody detection techniques, the incidence of NMOSD in different regions is still controversial. It is worth affirming that with the maturity of detection technology and the improvement of people's understanding of the disease, the incidence of the disease in various regions of the world is increasing year by year[1,2,3,4]. One study showed that in 100 patients with APS onset NMOSD, women were still more common, and the epidemiological data were similar to other NMOSD patients[5]. NMOSD has the characteristics of high recurrence rate and high disability rate in the course of disease, but the pathogenesis and recurrence factors are not completely clear. Multi-center studies have shown that NMOSD is related to genetics, environment, autoimmune, infection, climate and other factors, and its pathogenesis remains to be further explored[6,7].

In addition to the common optic neuritis and acute myelitis, patients with area postrema syndrome are often prone to missed diagnosis and misdiagnosis. APS can appear as an isolated clinical symptom in the early stage of the disease, often presenting as intractable nausea and vomiting. Therefore, APS is often seen in other departments other than neurology[8]. Among the 4 patients included this time, 3 were admitted to the Department of Gastroenterology at the onset of the disease, and 2 of them were not correct diagnosed and treated in time due to misdiagnosis, so their symptoms worsened and they needed to be transferred to ICU for life support. Therefore, it is of great importance to improve clinicians' understanding of the disease. The pathogenesis of APS is mainly related to aquaporin 4 antibody (AQP4-IgG). AQP4 is highly expressed in the nervous system, such as thalamus, hypothalamus, corpus callosum, periventricular, spinal cord, optic nerve and area postrema. The area postrema serves as the

nausea, vomiting and hiccup center, and vomiting-related chemical stimuli can cause nausea and vomiting by stimulating chemoreceptors in the area postrema[9,10]. In this paper, case 2 was misdiagnosed as cerebral infarction for many times and failed to receive timely diagnosis and treatment for a long time. A multi-center retrospective study in South Korea divided patients into early-onset NMOSD (EONMOSD, age of first onset ≤ 50 years) and late-onset NMOSD (LONMOSD) according to their age of onset. The results showed that age of onset was an important factor affecting the course of disease and clinical prognosis. In this study, 62.2% of LONMOSD patients presented with transverse myelitis and 37.2% presented with optic neuritis. Other clinical manifestations were rare[11]. Another study also supports this view, LONMOSD has fewer lesions around the fourth ventricle and more lesions in the cerebral hemisphere than EONMOSD[12]. By comparing 12 male LONMOSD patients and 64 female LONMOSD patients, other scholars found that the onset of transverse myelitis was less in males, the time from onset to diagnosis was shorter than that in females, and the EDSS score was lower[13]. Clinical diagnosis of NMOSD is often confused by gender, age of onset and atypical clinical manifestations. Some patients may have monoplegia or hemiplegia due to different lesion location, which needs to be differentiated from ischemic cerebrovascular disease.

In order to improve the diagnosis rate of APS, experts at home and abroad have reached a consensus on the diagnostic criteria of APS. Clinical acute or subacute intractable nausea, vomiting and/or hiccup, symptoms lasting more than 48 hours and excluding other causes, APS should be highly suspected, and the diagnosis can be confirmed after the improvement of AQP4 antibody test[5,14]. In recent years, some scholars for AQP4 antibody negative serum myelin oligodendrocytes glycoprotein (MOG) antibody positive patients study found that compared with the NMOSD AQP4 antibody positive patients, two kinds of antibody negative and MOG antibody positive patients rarely serious clinical symptoms, the prognosis is good, the APS MOG antibody positive patients rarely appear, This is consistent with our data[15,16]. There are markers in the imaging of APS patients, and the occurrence of "inverted V sign" in medulla oblongata segment on axial MRI has high specificity for the diagnosis of NMOSD. In addition, sagittal MRI of most APS patients also showed "linear sign", but "linear sign" were also seen in other diseases besides NMOSD[17,18]. Case 2 underwent cranial MRI procedures several times before the diagnosis, but no obvious lesions on the dorsolateral medulla oblongata were identified. These observations caution clinicians to consider the patients with intractable nausea and vomiting without apparent medulla oblongata lesions on the imaging for the diagnosis of central nervous system demyelinating diseases.

NMOSD patients are often associated with other autoimmune diseases, such as systemic lupus erythematosus and sjogren's syndrome[19]. Studies have found thymus degeneration in NMOSD patients, which may be an important cause of systemic immune dysfunction[20]. The positive antinuclear antibody was not significantly correlated with the course and severity of NMOSD, but the positive antinuclear antibody was more likely to be accompanied by the increase of other antibodies than the negative antinuclear antibody[21]. So far, no large sample studies have demonstrated the existence of specific autoimmune diseases among NMOSD patients with different clinical symptom onset.

The symptoms of most NMOSD patients improved after shock therapy with high dose steroid (HDS) [14], but a small number of patients were still insensitive to HDS. Patients who are not sensitive to HDS therapy during the acute attacks may be treated with intravenous immunoglobulin (IVIg), which reduces disability and prolongates the time to relapse[22]. In addition to IVIg, Immune adsorption (IA) and Plasma exchange (PE) have been suggested to be equally effective in the acute attacks[23]. Compared with IVMP alone, HDS combined with IVIg is superior to IVMP alone. Comparing the data of 243 patients with acute onset NMOSD, a study concluded that HDS combined with IVIg was superior to HDS alone in patients with EDSS > 6. However, continued use of IVIg does not improve the outcome of patients who do not respond to HDS treatment[24]. This may explain why case 1 in this study received IVIg and PE after HDS without significant clinical improvement.

Rituximab (RTX) is increasingly being used in the treatment of NMOSD by depleting CD20 and thereby suppressing the immune system. A number of studies have confirmed the safety and effectiveness of RTX, and the low incidence of adverse drug safety events and opportunistic infections is more advantageous than other therapeutic drugs[25,26,27]. In China, low-dose RTX is mostly used to prevent the recurrence of NMOSD. RTX can significantly reduce the recurrence rate of NMOSD and effectively improve the degree of disability of patients, but there are still a small number of patients with short-term recurrence after RTX application[28,29]. Some scholars believe that it takes time for RTX to eliminate pathogenic antibodies, and peripheral B cells are mainly affected, and a single course of RTX treatment cannot eliminate specific memory B cells[30,31]. In our study, case 1 did not monitor B cells during the application of low-dose RTX, so the dosage of RTX could not be adjusted, which may be one of the reasons for the short-term recurrence of the disease in the patient. Perhaps adjusting the dose of RTX treatment according to the number of B cells and individualizing the treatment plan are important means to reduce short-term recurrence of RTX treatment in the future.

Older age, shorter time between onset and first onset, and lack of Immunosuppressive therapy (IST) have been found to be associated with higher mortality, regardless of the severity of the onset[32]. According to the follow-up of 17 patients with NMOSD, 14 of them relapsed after six months of drug withdrawal, suggesting that patients with severe clinical symptoms before IST treatment should be carefully discontinued[33]. A Chinese single-center study also supports the view that more caution is needed when discontinuing IST, regardless of the duration of use[34]. Due to the existence of respiratory and cardiovascular centers in the upper cervical spinal cord and lower brain stem, the progression of medulla oblongata lesions in NMOSD patients is likely to endanger patients' lives. Therefore, NMOSD with area postrema syndrome as initial symptom should undergo careful clinical evaluation before careful discontinuation of drugs.

Clinically assessing whether a patient with NMOSD needs to stop treatment, intensify treatment, or initiate preventive treatment is difficult due to the lack of markers that can be used to predict disease. Levels of serum glial fibrillary acidic protein (sGFAP) were slightly higher in patients with NMOSD in clinical remission compared with healthy controls, and sGFAP was significantly higher in acute attacks compared with remission. SGFAP may be used as a biomarker of disease activity in remission in the

future. Higher sNfL levels were also found to indicate shorter onset time[35]. A prospective study in China suggested that sNfL could be used as a biomarker for the severity of NMOSD, and higher levels of TH-2-related cytokines (by antagonizing IL-1, IL-4, IL10 and IL-13 receptors) were involved in the process of disease remission[36]. In addition, IL-6, IL-10, C3 and C4 are thought to be involved in the occurrence of diseases and may become potential biomarkers for clinical diagnosis and treatment in the future[37,38,39,40].

5 Conclusion

The clinical manifestations of NMOSD are complex and diverse, and the initial symptoms, onset age and MRI can all affect clinicians' judgment of the disease. Early identification of APS and timely therapy can prevent visual and physical disabilities, even respiratory failure and cardiac arrest. Clinical withdrawal of NMOSD patients needs to be evaluated in many aspects. For patients with older onset and APS, the treatment course can be appropriately extended to reduce disease recurrence. It is necessary to strengthen the study of serum and imaging markers for predicting the progression and recurrence of the disease.

Declarations

Ethics approval and consent to participate

The studies have approved by The First Affiliated Hospital of Hainan Medical University Ethics Review Board. Informed consent was obtained from all patients included in the study.

Consent for publication

Not applicable.

Availability of data and materials

Data supporting these findings are available from the corresponding author upon request. The data cannot be made publicly available because of privacy or ethical restrictions.

Competing interests

All authors declare that they have no conflict of interests.

Funding

This project supported by the Hainan Province Clinical Medical Center.

Authors' contributions

Ting Liu, Lijuan Li, Lin Ma designed the study. Ting Liu, Binji Liang, Xian Li collected and prepared the patient information. Ting Liu, Lijuan Li, Lin Ma, Binji Liang, Xian Li interpreted the data. Ting Liu, Lijuan Li, Lin Ma drafted the manuscript. All of the authors critically reviewed and revised the manuscript, and final approval of the version to be published.

Acknowledgements

Not applicable.

References

- [1]Wang Kai-Chen., Tsai Ching-Piao., Lee Chao-Lin., Chen Shao-Yuan., Chen Shyi-Jou.(2011). The prevalence of long spinal cord lesions and anti-aquaporin 4 antibodies in neuromyelitis optica patients in Taiwan. *Eur Neurol*, 65(2), 99-104. doi:10.1159/000322740
- [2]Ochi Hirofumi., Fujihara Kazuo.(2016). Demyelinating diseases in Asia. *Curr Opin Neurol*, 29(3), 222-8. doi:10.1097/WCO.0000000000000328
- [3]Houzen Hideki.,Kondo Kimito.,Niino Masaaki,... & Tanaka Keiko.(2017).Prevalence and clinical features of neuromyelitis optica spectrum disorders in northern Japan.. *Neurology*(19), doi:10.1212/WNL.0000000000004611.
- [4]Fang Chen-Wen., Wang Hsin-Pei., Chen Ho-Min., Lin Jou-Wei., Lin Wei-Sheng.(2020). Epidemiology and comorbidities of adult multiple sclerosis and neuromyelitis optica in Taiwan, 2001-2015. *Mult Scler Relat Disord*, 45(undefined), 102425. doi:10.1016/j.msard.2020.102425
- [5]Shosha Eslam., Dubey Divyanshu., Palace Jacqueline., Nakashima Ichiro., Jacob Anu., Fujihara Kazuo., Takahashi Toshiyuki., Whittam Daniel., Leite Maria Isabel., Misu Tatsuro., Yoshiki Takai., Messina Silvia., Elson Liene., Majed Masoud., Flanagan Eoin., Gadoth Avi., Huebert Carey., Sagen Jessica., Greenberg Benjamin M., Levy Michael., Banerjee Aditya., Weinshenker Brian., Pittock Sean J.(2018). Area postrema syndrome: Frequency, criteria, and severity in AQP4-IgG-positive NMOSD. *Neurology*, 91(17), e1642-e1651. doi:10.1212/WNL.0000000000006392
- [6]Qiu Yuhan., Zhou Qiao., Du Qin., Chen Hongxi., Shi Ziyang., Zhang Ying., Wang Jiancheng., Yan Chao., Zhao Zhengyang., Yang Mu., Zhou Hongyu.(2020). Seasonal variation in relapse of neuromyelitis optica spectrum disorders: A retrospective study in China. *J Neuroimmunol*, 347(undefined), 577351. doi:10.1016/j.jneuroim.2020.577351
- [7] Papp Viktoria., Magyari Melinda., Aktas Orhan., Berger Thomas., Broadley Simon A., Cabre Philippe., Jacob Anu., Kira Jun-Ichi., Leite Maria Isabel., Marignier Romain., Miyamoto Katsuichi., Palace Jacqueline., Saiz Albert., Sepulveda Maria., Sveinsson Olafur., Illes Zsolt.(2021). Worldwide Incidence and Prevalence of Neuromyelitis Optica: A Systematic Review. *Neurology*, 96(2), 59-77. doi:10.1212/WNL.0000000000011153

- [8]Popescu B F Gh., Lennon V A., Parisi J E., Howe C L., Weigand S D., Cabrera-Gómez J A., Newell K., Mandler R N., Pittock S J., Weinshenker B G., Lucchinetti C F.(2011). Neuromyelitis optica unique area postrema lesions: nausea, vomiting, and pathogenic implications. *Neurology*, 76(14), 1229-37. doi:10.1212/WNL.0b013e318214332c
- [9]Pittock Sean J., Weinshenker Brian G., Lucchinetti Claudia F., Wingerchuk Dean M., Corboy John R., Lennon Vanda A.(2006). Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. *Arch Neurol*, 63(7), 964-8. doi:10.1001/archneur.63.7.964
- [10]Camara-Lemarroy Carlos R., Burton Jodie M.(2019). Area postrema syndrome: A short history of a pearl in demyelinating diseases. *Mult Scler*, 25(3), 325-329. doi:10.1177/1352458518813105
- [11]Seok Jin Myoung., Cho Hye-Jin., Ahn Suk-Won., Cho Eun Bin., Park Min Su., Joo In-Soo., Shin Ha Young., Kim Sun-Young., Kim Byung-Jo., Kim Jong Kuk., Cho Joong-Yang., Huh So-Young., Kwon Ohyun., Lee Kwang-Ho., Kim Byoung Joon., Min Ju-Hong.(2017). Clinical characteristics of late-onset neuromyelitis optica spectrum disorder: A multicenter retrospective study in Korea. *Mult Scler*, 23(13), 1748-1756. doi:10.1177/1352458516685416
- [12]Zhang Lin-Jie., Yang Li-Na., Li Ting., Wang Jing., Qi Yuan., Zhang Da-Qi., Yang Chun-Sheng., Yang Li.(2017). Distinctive characteristics of early-onset and late-onset neuromyelitis optica spectrum disorders. *Int J Neurosci*, 127(4), 334-338. doi:10.1080/00207454.2016.1254630
- [13]Liang Jie., Liu Jia., Gu Meifeng., Zhu Cansheng., Xu Xiaofeng., Fan Rong., Peng Fuhua., Jiang Ying.(2021). Clinical Characteristics of Chinese Male Patients with Aquaporin-4 Antibody-Positive Late-Onset Neuromyelitis Optica Spectrum Disorder. *Neuroimmunomodulation*, 28(2), 61-67. doi:10.1159/000515555
- [14]Wingerchuk Dean M., Banwell Brenda., Bennett Jeffrey L., Cabre Philippe., Carroll William., Chitnis Tanuja., de Seze Jérôme., Fujihara Kazuo., Greenberg Benjamin., Jacob Anu., Jarius Sven., Lana-Peixoto Marco., Levy Michael., Simon Jack H., Tenembaum Silvia., Traboulsee Anthony L., Waters Patrick., Wellik Kay E., Weinshenker Brian G., International Panel for NMO Diagnosis.(2015). International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*, 85(2), 177-89. doi:10.1212/WNL.0000000000001729
- [15]Hyun Jae-Won., Kwon Young Nam., Kim Sung-Min., Lee Hye Lim., Jeong Woo Kyo., Lee Hye Jung., Kim Byoung Joon., Kim Seung Woo., Shin Ha Young., Shin Hyun-June., Oh Sun-Young., Huh So-Young., Kim Woojun., Park Min Su., Oh Jeeyoung., Jang Hyunmin., Park Na Young., Lee Min Young., Kim Su-Hyun., Kim Ho Jin.(2020). Value of Area Postrema Syndrome in Differentiating Adults With AQP4 vs. MOG Antibodies. *Front Neurol*, 11(undefined), 396. doi:10.3389/fneur.2020.00396
- [16]Du Qin., Shi Ziyang., Chen Hongxi., Zhang Ying., Wang Jiancheng., Qiu Yuhang., Zhao Zhengyang., Zhang Qin., Zhou Hongyu.(2021). Comparison of clinical characteristics and prognoses in patients with

different AQP4-Ab and MOG-Ab serostatus with neuromyelitis optica spectrum disorders. *J Neuroimmunol*, 353(undefined), 577494. doi:10.1016/j.jneuroim.2021.577494

[17]Zhou Chenguang., He Yuanhong., Gao Xiaoya., Zhu Yinghui., Chao Zhiwen., Wang Xingping.(2018). Neuromyelitis optical spectrum disorders presenting with isolated "inverted V" sign in area postrema. *Neurol Sci*, 39(7), 1299-1301. doi:10.1007/s10072-018-3302-9

[18]Zhou C., Liao L., Sun R., Wang J., Di W., Zhu Y., He Y.(2021). Area postrema syndrome as initial manifestation in neuromyelitis optica spectrum disorder patients: A retrospective study. *Rev Neurol (Paris)*, 177(4), 400-406. doi:10.1016/j.neurol.2020.07.019

[19]Martín-Nares E., Hernandez-Molina G., Fragoso-Loyo H.(2019). Aquaporin-4-IgG positive neuromyelitis optica spectrum disorder and systemic autoimmune diseases overlap syndrome: a single-center experience. *Lupus*, 28(11), 1302-1311. doi:10.1177/0961203319877255

[20]Chang Haoxiao., Cong Hengri., Wang Huabing., Du Li., Tian De-Cai., Ma Yuetao., Xu Yun., Wang Yupeng., Yin Linlin., Zhang Xinghu.(2021). Thymic Involution and Altered Naive CD4 T Cell Homeostasis in Neuromyelitis Optica Spectrum Disorder. *Front Immunol*, 12(undefined), 645277. doi:10.3389/fimmu.2021.645277

[21]Lee Eun-Jae., Lim Young-Min., Kim Sun-Young., Lee JooKyung., Kim Hyunjin., Jin Joo Yea., Oh Yeo Jin., Kim Kwang-Kuk.(2019). The clinical and prognostic value of antinuclear antibodies in NMO-IgG seropositive neuromyelitis optica spectrum disorder. *J Neuroimmunol*, 328(undefined), 1-4. doi:10.1016/j.jneuroim.2018.11.012

[22]Lin Jie., Xue Binbin., Zhu Ruofan., Pan Juyuan., Li Jia., Lin Yan., Li Xiang., Xia Junhui.(2021). Intravenous immunoglobulin as the rescue treatment in NMOSD patients. *Neurol Sci*, undefined(undefined), undefined. doi:10.1007/s10072-021-05079-4

[23]Li Rui., Wang Jingqi., Li Cong., Liu Xiangfu., Chu Muyang., Chang Yanyu., Wang Yuge., Wang Xia., Yu Boguang., Ling Li., Yang Hui., Yang Huan., Hu Xueqiang., Qiu Wei.(2021). Rescue immunoadsorption treatment for neuromyelitis optica spectrum disorder attacks unresponsive to intravenous methylprednisolone. *J Neuroimmunol*, 356(undefined), 577604. doi:10.1016/j.jneuroim.2021.577604

[24]Li Xindi., Tian De-Cai., Fan Moli., Xiu Yuwen., Wang Xinli., Li Ting., Jia Dongmei., Xu Wangshu., Song Tian., Shi Fu-Dong., Zhang Xinghu.(2020). Intravenous immunoglobulin for acute attacks in neuromyelitis optica spectrum disorders (NMOSD). *Mult Scler Relat Disord*, 44(undefined), 102325. doi:10.1016/j.msard.2020.102325

[25]Kim Su-Hyun., Kim Woojun., Li Xue Feng., Jung In-Ja., Kim Ho Jin.(2011). Repeated treatment with rituximab based on the assessment of peripheral circulating memory B cells in patients with relapsing neuromyelitis optica over 2 years. *Arch Neurol*, 68(11), 1412-20. doi:10.1001/archneurol.2011.154

- [26]Mealy Maureen A., Wingerchuk Dean M., Palace Jacqueline., Greenberg Benjamin M., Levy Michael. (2014). Comparison of relapse and treatment failure rates among patients with neuromyelitis optica: multicenter study of treatment efficacy. *JAMA Neurol*, 71(3), 324-30. doi:10.1001/jamaneurol.2013.5699
- [27]Novi Giovanni., Bovis Francesca., Capobianco Marco., Frau Jessica., Mataluni Giorgia., Curti Erica., Zuliani Luigi., Cavalla Paola., Brambilla Laura., Annovazzi Pietro., Repice Anna Maria., Lanzillo Roberta., Esposito Sabrina., Benedetti Luana., Maietta Ilaria., Sica Francesco., Buttari Fabio., Malucchi Simona., Fenu Giuseppe., Landi Doriana., Bosa Chiara., Realmuto Sabrina., Malentacchi Maria., Granella Franco., Signori Alessio., Bonavita Simona., Uccelli Antonio., Sormani Maria Pia., iMUST group.(2019). Efficacy of different rituximab therapeutic strategies in patients with neuromyelitis optica spectrum disorders. *Mult Scler Relat Disord*, 36(undefined), 101430. doi:10.1016/j.msard.2019.101430
- [28]Wang Yupeng., Chang Haoxiao., Zhang Xinghu., Yin Linlin.(2021). Efficacy of rituximab in the treatment of neuromyelitis optica spectrum disorders: An update systematic review and meta-analysis. *Mult Scler Relat Disord*, 50(undefined), 102843. doi:10.1016/j.msard.2021.102843
- [29]Zhang Meini., Zhang Chuntao., Bai Peng., Xue Huiru., Wang Guilian.(2017). Effectiveness of low dose of rituximab compared with azathioprine in Chinese patients with neuromyelitis optica: an over 2-year follow-up study. *Acta Neurol Belg*, 117(3), 695-702. doi:10.1007/s13760-017-0795-6
- [30]Shi Bingxin., Zhao Mangsuo., Qiao Liyan., Huang Fangjie., Zhou Shimei., Wei Yan., Wang Jing., Wang Ning.(2021). Relapses shortly after rituximab treatment in neuromyelitis optica spectrum disorder. *Mult Scler Relat Disord*, 54(undefined), 103143. doi:10.1016/j.msard.2021.103143
- [31]Maurer Michael A., Tuller Friederike., Gredler Viktoria., Berger Thomas., Lutterotti Andreas., Lünemann Jan D., Reindl Markus.(2016). Rituximab induces clonal expansion of IgG memory B-cells in patients with inflammatory central nervous system demyelination. *J Neuroimmunol*, 290(undefined), 49-53. doi:10.1016/j.jneuroim.2015.11.006
- [32]Du Qin., Shi Ziyang., Chen Hongxi., Zhang Ying., Wang Jiancheng., Qiu Yuhang., Zhao Zhengyang., Zhang Qin., Zhou Hongyu.(2021). Mortality of neuromyelitis optica spectrum disorders in a Chinese population. *Ann Clin Transl Neurol*, 8(7), 1471-1479. doi:10.1002/acn3.51404
- [33]Kim Su-Hyun., Jang Hyunmin., Park Na Young., Kim Yeseul., Kim So-Yeon., Lee Min Young., Hyun Jae-Won., Kim Ho Jin.(2021). Discontinuation of Immunosuppressive Therapy in Patients With Neuromyelitis Optica Spectrum Disorder With Aquaporin-4 Antibodies. *Neurol Neuroimmunol Neuroinflamm*, 8(2), undefined. doi:10.1212/NXI.0000000000000947
- [34]Li Cong., Wang Jingqi., Sun Xiaobo., Li Rui., Chang Yanyu., Wang Yuge., Zhong Xiaonan., Kermode Allan G., Mao Zhifeng., Qiu Wei.(2021). The current situation of diagnosis and treatment of neuromyelitis optica spectrum disorder: Experience with 461 cases from a single centre in South China. *J Neuroimmunol*, 353(undefined), 577506. doi:10.1016/j.jneuroim.2021.577506

- [35]Schindler Patrick., Grittner Ulrike., Oechtering Johanna., Leppert David., Siebert Nadja., Duchow Ankelien S., Oertel Frederike C., Asseyer Susanna., Kuchling Joseph., Zimmermann Hanna G., Brandt Alexander U., Benkert Pascal., Reindl Markus., Jarius Sven., Paul Friedemann., Bellmann-Strobl Judith., Kuhle Jens., Ruprecht Klemens.(2021). Serum GFAP and NfL as disease severity and prognostic biomarkers in patients with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder. *J Neuroinflammation*, 18(1), 105. doi:10.1186/s12974-021-02138-7
- [36]Wang Jingqi., Cui Chunping., Lu Yaxin., Chang Yanyu., Wang Yuge., Li Rui., Shan Yilong., Sun Xiaobo., Long Youming., Wang Honghao., Wang Zhanhang., Lee Michael., He Shane., Lu Zhengqi., Qiu Wei., Tan Sha.(2021). Therapeutic Response and Possible Biomarkers in Acute Attacks of Neuromyelitis Optica Spectrum Disorders: A Prospective Observational Study. *Front Immunol*, 12(undefined), 720907. doi:10.3389/fimmu.2021.720907
- [37]Li Rui., Wang Jingqi., Li Cong., Liu Xiangfu., Chu Muyang., Chang Yanyu., Wang Yuge., Wang Xia., Yu Boguang., Ling Li., Yang Hui., Yang Huan., Hu Xueqiang., Qiu Wei.(2021). Rescue immunoadsorption treatment for neuromyelitis optica spectrum disorder attacks unresponsive to intravenous methylprednisolone. *J Neuroimmunol*, 356(undefined), 577604. doi:10.1016/j.jneuroim.2021.577604
- [38]Wei Yuzhen., Chang Haoxiao., Li Xindi., Wang Huabing., Du Li., Zhou Heng., Xu Wangshu., Ma Yuetao., Yin Linlin., Zhang Xinghu.(2018). Cytokines and Tissue Damage Biomarkers in First-Onset Neuromyelitis Optica Spectrum Disorders: Significance of Interleukin-6. *Neuroimmunomodulation*, 25(4), 215-224. doi:10.1159/000494976
- [39]Baek Seol-Hee., Kim Boram., Shin Je-Young., Choi Seok-Jin., Ahn So Hyun., Choi Youn Soo., Kim Sung-Min., Sung Jung-Joon.(2021). EB12-expressing B cells in neuromyelitis optica spectrum disorder with AQP4-IgG: Association with acute attacks and serum cytokines. *J Neuroimmunol*, 358(undefined), 577637. doi:10.1016/j.jneuroim.2021.577637
- [40]Pache Florence., Ringelstein Marius., Aktas Orhan., Kleiter Ingo., Jarius Sven., Siebert Nadja., Bellmann-Strobl Judith., Paul Friedemann., Ruprecht Klemens.(2021). C3 and C4 complement levels in AQP4-IgG-positive NMOSD and in MOGAD. *J Neuroimmunol*, 360(undefined), 577699. doi:10.1016/j.jneuroim.2021.577699

Figures

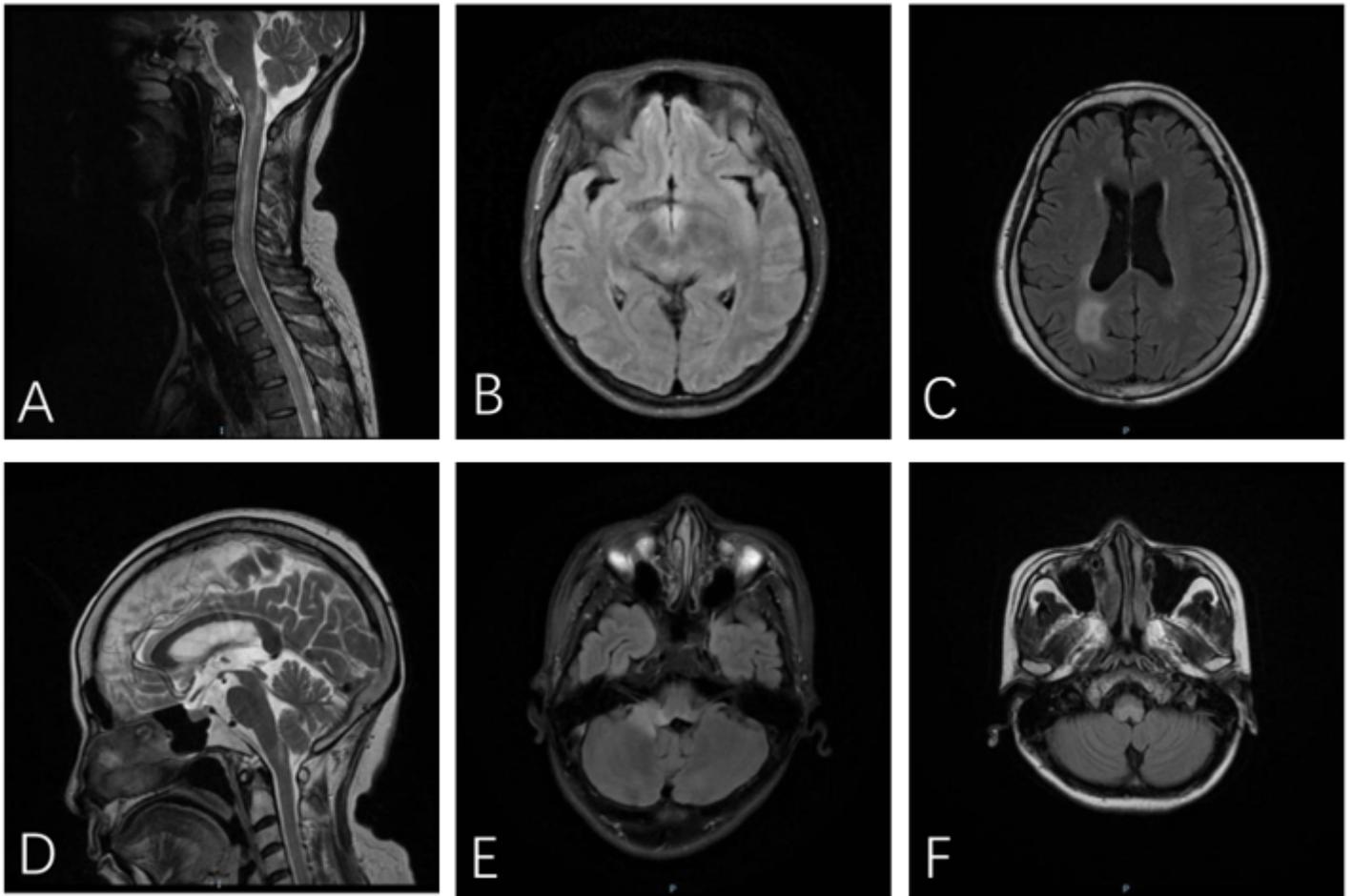


Figure 1

the MRI of case 1 is A-B, the MRI of case 2 is C-D, the MRI of case 3 is E, the MRI of case 4 is F. Figure A shows medulla oblongata, cervical medulla, and thoracic medulla with hyperintense signal. Figure B shows bilateral hypothalamus with hyperintense signal. Figure C shows hyperintense signal in paraventricular. Figure D shows hyperintense signal in the medulla oblongata. Figure E shows right cerebellum and brainstem with hyperintense signal. Figure F shows hyperintense signal in the dorsal medulla oblongata.