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Importance of Regular and Maintenance Therapy Adherence in Neuromyelitis Optica (NMO): Lessons from a Repeating Relapse Case

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Patient: Female, 58
Final Diagnosis: NMO
Symptoms: New-onset right leg weakness and pain
Medication: —
Clinical Procedure: Progressive and recurring
Specialty: Neurology

Objective: Rare disease
Background:





Neuromyelitis optica (NMO) is a rare demyelinating disease of the central nervous system; NMO predominantly affects the spinal cord and optic nerves. The diagnosis is based on history, clinical presentation, seropositive NMO-IgG antibody, and notably, exclusion of other diseases. Despite the absence of definitive therapeutic strategies for NMO, methylprednisolone pulse therapy and plasma exchange are used for acute phase treatment, while immunosuppressive agent(s) are recommended to prevent relapses and improve prognosis. Here, we report a repeating relapse NMO case due to lack of regular and maintenance therapy.

Case Report: A 58-year-old female with chronic NMO presented with a three-day history of new-onset right leg weakness and pain. The patient was diagnosed with NMO three years ago and presented with her fourth attacks. During her initial diagnosis, she was initiated on steroids. One year later, she developed the first relapse and was treated with steroids and rituximab, leading to 1.5-year remission. After the second relapse, steroids and rituximab was still given as maintenance therapy, but was not followed. Thus, the third relapse occurred in five months. During this hospitalization, she received initially high-dose solumedrol (1 g daily for five days) in addition to gabapentin 100 mg (gradually increased to 300 mg) three times a day for muscle spasms. Due to worsening of paresthesia and hemiparesis, it was decided to place her on plasma exchange treatment. After two plasma exchanges, the patient's condition was improved and she regained strength in her lower extremity. She completed five more cycles of plasma exchange, and was then discharged on steroid therapy (prednisone 20 mg daily for 10 days then taper) as maintenance therapy and with follow-up in neurology clinic.

Conclusions: Over the span of three years, the patient has had three relapses since her NMO diagnosis where her symptoms have worsened. Steroid therapy alone seemed not insufficient in managing her more recent relapses. Nonadherence to NMO treatment likely increased her risk for recurrence, thus regular and long-term maintenance therapy is imperative to delay the progression and prevent relapse in NMO.

MeSH Keywords: Immunosuppressive Agents • Methylprednisolone • Neuromyelitis Optica • Plasma Exchange • Recurrence

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Background

Neuromyelitis optica (NMO), also known as Devic's syndrome, is a rare demyelinating disease of the central nervous system (CNS) characterized by severe, autoimmune inflammation-mediated demyelination and axonal damage, predominantly affecting the spinal cord and optic nerves [1]. NMO is more common in females than males. Particularly, recurrent NMO is ten times more prevalent in females than males. Although any age group may be affected, the median age of patients diagnosed with NMO is approximately 30 years of age [1,2].

Classically, acute attacks of NMO include optic neuritis leading to visual loss and eye pain, and transverse myelitis resulting in limb weakness and potentially paraplegia/quadriplegia, bladder dysfunction, and a spinal cord sensory loss [2–4]. In some relapsing patients, both optic neuritis and transverse myelitis present simultaneously. Unilateral optic neuritis is commonly involved, but a sequential optic neuritis or bilateral simultaneous optic neuritis also frequently occurs [2–4]. Transverse myelitis generally presents over several hours or days, but in the absence of structural spinal cord abnormality [5,6]. Brain stem symptoms i.e., nausea, vomiting, and hiccups are also commonly seen in NMO patients due to medullary involvement and may lead to acute neurogenic respiratory failure and death [7]. Additionally, there may be muscle involvement in NMO that presents as weakness with associated elevated muscle enzyme labs [5]. Truncal and lower extremity pain is another common symptom in NMO patients [5]. NMO should be distinguished from other CNS demyelination diseases, particularly multiple sclerosis (MS). Early discrimination between NMO and MS is necessary due to their different natural histories and treatment regimens [8–10]. NMO is an autoimmune inflammatory disease, a specific NMO-IgG antibody targeted to aquaporin-4 (AQP4) is found in the majority of NMO patients [11]. Therefore, NMO can be diagnosed confidently based on the patient's history, clinical manifestations, seropositive NMO-IgG antibody, and exclusion of other disorders.

NMO is a progressive and relapsing disease that has poor prognosis and outcomes if not treated immediately [6,7,12]. Despite the absence of a definitive therapeutic strategy for NMO, current guidelines recommend methylprednisolone pulse therapy and plasma exchange in the acute phase [13,14]. To prevent relapses and improve outcome, at least one immunosuppressive agent, such as oral glucocorticoids, azathioprine, methotrexate, mycophenolate mofetil, or rituximab should be initiated for maintenance therapy and continued for approximately five years after the initial presentation [15–17].

Here, we report a repeating relapse NMO case of a patient who has previously presented with four relapses over a span of three years. Lack of regular and maintenance therapy emphasizes

the importance of adherence to regular and long-term maintenance therapy in NMO.

Case Report

Chief complaint

A 58-year-old African American female presented to our hospital in September 2016 with new-onset right leg weakness and bilateral leg pain for three days. The patient described the pain as sharp, tingling, and shooting in nature. It initially presented in her knees and migrated to her hips, where it then radiated down the back of her right leg. The patient stated that she took 650 mg of acetaminophen three times, but the pain completely debilitated her to the point where she was unable to ambulate. She also complained of burning pain and weakness of her left upper extremity (LUE) for several months. Of note, sequela of her other flares has left her with severe visual impairment of her right eye and she is legally blind in her left eye. At the time of presentation, the patient was not on any disease modifying therapy.

Past NMO history and treatment (Table 1)

This patient initially presented with pain, blurriness, and vision loss in her left eye in October 2013. She was diagnosed with NMO in January 2014 due to positive NMO-IgG antibody in cerebrospinal fluid (CSF). Other lab tests including MPO, ANA, HLA-B27, RF, and FTA ABS were negative or normal (Table 1). MS was suspected but excluded by magnetic resonance imaging (MRI) in brain and spine (Table 2). She was given a three-day course of intravenous (IV) solumedrol (methylprednisolone 1 g) and then transitioned to oral steroid (prednisone 20 mg daily) with tapering.

The first relapse occurred in November 2014 when she presented with right eye pain and vision loss. She was treated with five days of IV methylprednisolone 1 g daily and five days of IV immunoglobulin (IVIG). Following prednisone tapering, two doses of rituximab 1 g were given on 09/23/2015 and 10/7/2015 as maintenance therapy.

On routine check-up on 12/15/2015, she was on prednisone 10 mg daily. Examination showed bilateral vision loss, but without signs of myelitis. She was tapering prednisone from 10 mg daily to 5 mg for two weeks and then 2.5 mg for two more weeks. Two doses of rituximab have been planned for her in 03/2016, but she did not follow this recommendation.

The second relapse occurred in April 2016 when she presented with left paresthesia. She was treated with five days of IV methylprednisolone 1 g daily. Then, oral prednisone 20 mg

Table 1. The attack and relapse history, and corresponding treatment strategies in NMO patient.

Key time point	Presentation	Lab results	Treatment in hospital	Maintenance therapy
10/2013 (first attack)	Losing vision of the left eye with pain and blurriness; no other symptoms	RPR (-), ANA (-), MPO (-), proteinase (-), HLA-B27 (-), FTA ABS (-), RF (8)	3 days of IV solumedrol 1 g daily with some mild improvement	Oral steroid (prednisone 20 mg daily) then taper
01/2014	NMO was diagnosed by neuro-ophthalmologist	CSF: NMO Ab (+); excluded MS by MRI		
11/2014 (first relapse)	Started losing vision in the right eye with eye pain	None	5 days of IV solumedrol 1g daily and 5 days of IVIG	Prednisone tapering; 2 doses of rituximab 1 g on 9/23/2015 and 10/7/2015
12/2015	Substantial bilateral vision loss, particularly left eye; Note: Between 11/2014 and 12/2015, her condition was relatively stable due to currently on the treatment with steroid and rituximab.	None	none	Cyclobenzaprine 10 mg twice a day; oral prednisone 10 mg daily and tapering 5 mg for 2 weeks and then 2.5 mg for 2 more weeks. Planned to give 2 doses of rituximab in 03/2016 (but not followed by patient)
04/2016 (second relapse)	Left paresthesia	None	5 days of IV solumedrol 1g daily	Oral steroids (prednisone 20 mg daily) and tapering afterward (but not followed by patient); Not on IS (refused by patient)
09/2016 (third relapse; admitted to our hospital)	New-onset right leg weakness and pain for 3 days; worsening left paresthesia	None	5 days of IV solumedrol 1g daily; prednisone 60 mg and tapered over 6 days; then re-initiated IV solumedrol for 5 more days; 7 plasma exchange	Discharged to rehab facility; prednisone 20 mg daily for 10 days then taper. Emphasized the importance of long-term therapy and follow-up with outpatient neurologist

RPR – rapid plasma regain test; ANA – antinuclear antibody; MPO – myeloperoxidase; HLA-B27 – human leukocyte antigen B27; FTA-ABS – fluorescent treponemal antibody absorption test; NMO Ab – neuromyelitis optica antibody; RF – rheumatoid factor; CSF – cerebrospinal fluid; IV – intravenous; solumedrol: methylprednisolone; MS – multiple sclerosis; IVIG – intravenous immunoglobulin; IS – immunosuppressant.

Table 2. Magnetic resonance imaging (MRI) results of NMO patient.

Routine MRI	Impression
Brain and orbits	Several non-enhancing T2 hyperintense lesions of the brain including the periventricular and subcortical white matter, brainstem, and brachium pontis. Punctate restricted diffusion may be associated with a right pontine lesion. Suspected volume loss of the left aspect nerve involving the cisternal and chiasmatic segment; there is no optic nerve swelling or optic nerve enhancement
Cervical spine and thoracic spine	Multiple segmental foci of intramedullary signal abnormality within the cervical and thoracic spinal cord without abnormal enhancement. Imaging findings are indicative of demyelinating process

daily with tapering was started for maintenance therapy. Of note, she did not follow the steroid tapering recommendation and refused rituximab. She opted to take holistic medicine.

The third relapse rapidly occurred in September 2016, presenting with new-onset right leg weakness and pain as well as worsening left paresthesia as described in the Chief Complaint. The patient was started on IV methylprednisolone 1 g daily for five days, gabapentin 100 mg three times a day, which was later increased to 300 mg three times a day following complaints of tingling and burning sensation in her feet, baclofen 10 mg three times a day for muscle spasms, and a proton pump inhibitor (pantoprazole 40 mg, daily) for gastrointestinal (GI) prophylaxis. Despite the high-dose steroids therapy, her symptoms failed to improve. Therefore, the patient was re-initiated with five more days of methylprednisolone, and plasma exchange therapy was considered. After two exchanges, the patient's condition was improved. She regained lower extremity strength. She received five additional cycles of plasma exchanges and was then discharged to a rehabilitation facility. For maintenance therapy, she was asked to take oral prednisone 20 mg daily for 10 days then tapering. She still refused to take rituximab though she the recommendation emphasized the importance of immunosuppressant. In addition, she was asked to adhere to the steroid therapy and follow-up with the outpatient neurologist.

The attack and relapse history, and the corresponding treatment strategies in this NMO patient are summarized in Table 1.

Past medical and family history

The patient had a history of hypertension and arthritis in bilateral knees. Her home medications included amlodipine 10 mg daily, acetaminophen/codeine 300 mg/30 mg as needed for pain, and baclofen 10 mg three times a day as needed for muscle spasms. No other family member was noted to have a history of neurological disease or any autoimmune disease. Ciprofloxacin was reported to give her hives. The patient denied any recent trauma, chest pain, shortness of breath, focal neuro deficits, and nausea or vomiting. A review of systems was negative for fever, rash, sore throat, dysuria, and active bleeding.

Physical examination

This patient was alert and oriented to person, place, and time. Her speech was fluent. Her face was symmetrical and her tongue was in midline. Her left eye visual fields were blind without color perception. Her right eye vision ability was 20/200. Bilateral extraocular movements were intact.

Motor: Strength testing revealed a pain-limited left upper extremity (LUE) strength 2/5 (limited by pain), right upper extremity (RUE) strength 5/5, left lower extremity (LLE) strength 1/5, and effort-dependent right lower extremity (RLE) strength 2/5 (effort dependent). Plantar reflexes were absent. Sensory examination was intact to pin and vibration. She was noticed to have swollen left hand and stiffness, in addition to bilateral leg pain. There was an increase in sensation on the left hemibody compared to her right side. All other neurological testing was normal. Her cerebellum/gait examination was deferred. Other examinations, including heart and lungs, were normal.

Throughout her admission, the patient remained quadriplegic with minimal improvement in her mobility of her bilateral feet and left arm. At discharge, she was able to rotate her right leg in the plane of the bed; her left leg could trace activation. She was able to move her digits slightly. She was able to slightly dorsiflex and plantarflex her right foot, move her left big toe and elevate her left arm a few inches in the air.

Discussion

The patient case we report here had a diagnosis of NMO based on her previous medical history, clinical manifestations, seropositive NMO-IgG antibody, and exclusion of MS by MRI. NMO, also known as Devic's syndrome, is a heterogeneous condition consisting of the simultaneous inflammation and demyelination of the optic nerve and the spinal cord [18]. Based on the presence of autoantibodies against AQP4, at least two different causes of NMO are proposed currently [18]. NMO-IgG, usually referred to as anti-AQP4 IgG, is present in 80% of NMO patients, and has been found to be able to distinguish NMO from standard MS. The discovery of NMO-IgG has opened a new way for investigating the causes of NMO. Besides AQP4-seropositive NMO, some AQP4-negative NMO are identified as the presence of anti-MOG (myelin oligodendrocyte), anti-connexin-43, or anti-AQP1. In addition, idiopathic NMO is defined by the absence of all the aforementioned antibodies [19,20]. Accordingly, the patient case that we reported here was NMO-IgG-positive. In a study with 132 of NMO patients, 73% were NMO-IgG positive and 11% were MOG-Ig positive. Of note, approximately half (42%) of AQP4-seronegative NMO cases were MOG-Ig seropositive [21]. Recently, it was reported that STAT4 polymorphisms were associated with NMO [22].

NMO can be monophasic or occur as a single episode with permanent remission. However, at least 85% of NMO patients experience repeated attacks [23]. Approximately 20% of patients with monophasic NMO have permanent visual loss, and 30% have permanent paralysis in one or both legs. Nevertheless, among patients with repeated relapsing NMO, 50% have paralysis or blindness within five years. Unfortunately, in some

repeated NMO patients, transverse myelitis in the cervical spinal cord occurred and resulted in respiratory failure and subsequent death [23]. These data demonstrate that NMO has a poor prognosis and each attack or relapse may aggravate symptoms. A similar disease course was observed in our patient, who initially presented with visual loss of one eye, but afterwards, two eyes were involved, and leg weakness was present. It has been reported that relapse generally occurs in the early disease course. Around 50% of NMO patients relapse within the first year of the initial event and about 75% within two-to-three years [23]. In our case report, the patient experienced three relapses over three years. Therefore, treatment, particularly long-term effective and persistent treatment in repeated cases, is a big challenge for NMO patients to prevent progression and improve prognosis.

Commonly, acute attacks are treated with short courses of high-dosage IV corticosteroids such as methylprednisolone. Plasmapheresis or plasma exchange is an effective treatment when attacks progress or do not respond to corticosteroid treatment [14,24–27]. As described in the literature, the combination of high-dosage IV methylprednisolone and plasma exchange in this patient quickly restored her neurologic function and promoted her recovery; presenting with improvement of her legs and arms motion following treatment.

Although no controlled trials have demonstrated the effectiveness of treatments for the prevention of attacks and/or relapses, many clinicians agree that long-term immunosuppression is required to reduce the frequency and severity of attacks [28]. Following successful treatment of an acute attack, low-dosage prednisone is effective in preventing NMO attacks [15,29], however, as a consequence, many NMO patients become steroid-dependent or resistant [15]. Long-term (about 5-years) maintenance therapy with immunosuppressants, such as azathioprine, rituximab, mycophenolate mofetil, mitoxantrone, and methotrexate, are recommended, particularly for NMO-IgG-positive patients [15,29,30]. It has been reported that oral glucocorticoids with one immunomodulatory agent, either azathioprine or cyclosporine, has better efficacy to maintain remission and prevent relapses [15,29]. In one NMO case, treatment with a combination of oral glucocorticoids and azathioprine resulted in relapse-free symptoms for over one year [26,27]. One study in Chinese patients with NMO provided evidence supporting the use of azathioprine plus a low-dose corticosteroid as an effective and safety strategy which was also associated with a reduction in the risk of relapse [31]. In Caucasian NMO patients with two-year follow-up, retreatment with rituximab every six months led to a reduction of the annualized relapse rate and of the median expanded disability status scale, indicative of a curative effect with a good safety profile [32]. Similarly, treatment of NMO with rituximab in Indian patients reduced the mean annualized relapse rate from

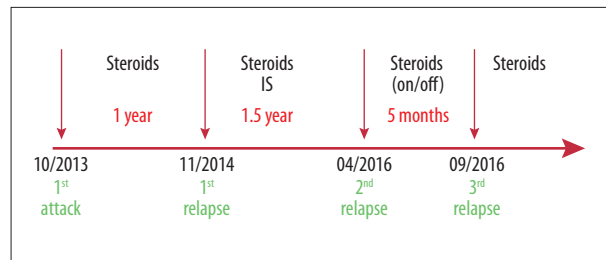


Figure 1. Schematic of relapse and treatment in the NMO patient. The first attack was treated with steroid with one-year remission. Following the first relapse, steroid and immunosuppressant (IS – rituximab) was given for maintenance therapy, leading to 1.5-year remission. After the second relapse, steroid was still given but recommend regimen was not followed well. The patient refused rituximab. Therefore, the third relapse occurred rapidly, within five months.

2.61 to 0.99 [33]. However, it was reported that two refractory NMO patients showed not only no response to rituximab, but also worsened symptoms after treatment [34]. In a small proportion of patients with refractory NMO, rituximab may either fail or induce rapid relapse of NMO. Although some evidence suggests that tocilizumab and eculizumab are associated with improvement in a small number of refractory NMO patients who have failed standard therapy [35,36], new treatment strategies still needed to be consider for refractory NMO.

Over the past three years, our patient relapsed three times. Her first attack was treated with steroids alone and her condition was relatively stabilized for about one year. Then the first relapse occurred, and the patient was treated with steroids and rituximab, thus she obtained 1.5-year remission. Due to failure to continue using rituximab, her second relapse occurred. Although she was asked to take steroids and rituximab, she did not take steroids regularly and stopped rituximab herself. The third relapse thus occurred rapidly after five months (Figure 1). Accordingly, her relapse and treatment history suggest that long-term maintenance therapy with a combination of steroid and immunosuppressive agents is very important for avoiding or reducing relapses, delaying progression, and improving outcome and prognosis in NMO. Furthermore, patients need to be counseled and educated about the disease, the disease course, and management strategies. Her treatment planning and recommendations emphasized that long-term therapy and follow-up were imperative for her condition, and in addition, potential benefits of therapy should be weighed against the risk of long-term toxicity of the agent (e.g., increased risk of relapse is common within the first two-to-three years). Additionally, physician should assess duration of treatment, history of relapse (frequency, severity, and recovery), treatment toxicity (actual or potential), and other factors (e.g., a woman's desire to become pregnant) when deciding when to discontinue therapy.

Finally, another big challenge is how to monitor or predict relapse of NMO. Monitoring NMO-IgG antibody titer may be useful for monitoring disease course although the antibody titers do not predict disease severity or individual patient thresholds for relapse [15]. In an international collaboration study involving a large number of NMO patients, treatment with either rituximab or mycophenolate mofetil was effective regardless of NMO-IgG serology status [37], suggesting that treatment should not differ. It was reported that the level of CD59 in cerebrospinal fluid was higher in NMO patients than those patients with non-inflammatory neurological disorders, and decreased in NMO after treatment [38]. Therefore, non-invasive biomarkers should be further investigated to monitor and/or predict relapse of NMO.

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Conclusions

Our NMO patient case had repeated relapses over the three years following her first attack. Her symptoms unfortunately worsened and she developed new-onset right leg weakness that we were not able to manage with high-dose steroids therapy alone, requiring the use of plasma exchange. Her repeating relapses are exacerbated by her medication nonadherence, thus emphasizing the importance of adherence to long-term regular and maintenance therapy with immunosuppressant in NMO.

Conflict of interest

None.