

# Cortical blindness and not optic neuritis as a cause of vision loss in a Sjögren's syndrome (SS) patient with the neuromyelitis optica spectrum disorder (NMOSD)

## Challenges of ascribing demyelinating syndromes to SS: a case report

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### Abstract

**Rationale:** The conception that multiple sclerosis may be challenging to distinguish from demyelinating manifestations of Sjögren's Syndrome (SS) was introduced more than 30 years ago. However, it is now recognized that the neuromyelitis optica spectrum disorder (NMOSD) may occur more frequently in SS as opposed to multiple sclerosis. Characteristic NMOSD features can include severe attacks of optic neuritis, myelitis which is frequently longitudinally-extensive (spanning at least three vertebral segments on magnetic resonance imaging [MRI]), and an association with anti-aquaporin-4 antibodies. In addition, whereas NMOSD was initially thought to spare the brain, it is now recognized that brain lesions occur in a majority of NMOSD patients. Therefore, it is important for the multi-disciplinary team of physicians who care for SS patients to understand this widening spectrum of NMOSD as encompassing brain lesions. In this case-report we describe clinical features, radiographic findings, and treatment of a SS NMOSD patient presenting with severely decreased visual acuity, visual hallucinations, and encephalopathy.

**Patient concerns:** The SS NMOSD patient presented with rapid, bilateral onset of severely decreased visual acuity and was therefore suspected as having bilateral optic neuritis.

**Diagnosis:** However, the patient lacked stigmata of optic neuritis, instead had visual hallucinations and encephalopathy suggestive of cortical blindness, and was noted to have occipital lobe lesions on brain MRI. Other radiographic findings included simultaneous enhancement of brainstem and periventricular lesions.

**Interventions:** The patient was initially treated with methylprednisolone with no change in her neurological deficits. She was then treated with plasma exchange therapy.

**Outcomes:** The patient had resolution of decreased visual acuity, visual hallucinations, encephalopathy, and contrast-enhancing brain lesions in response to plasma exchange therapy.

**Lesson:** We provide the first example of severely decreased visual acuity in a NMOSD patient due to cortical blindness and not bilateral optic neuritis. This finding expands the spectrum of central nervous system syndromes and brain lesions which may occur in NMOSD. The synchronous enhancement of a brainstem lesion (known to occur in NMOSD) with occipital lobe lesions also suggests that our patient's occipital lobe findings were due to NMOSD. All of our patient's findings had an excellent clinical and radiographic response to plasma exchange therapy.

**Abbreviations:** ACR/EULAR = American College of Rheumatology/European League Against Rheumatism, AQP4 = Aquaporin-4, CNS = Central nervous system, ELISA = enzyme-linked immunosorbent assay, LETM = Longitudinally-extensive transverse myelitis, mg = milligrams MRI = Magnetic resonance imaging, MS = Multiple sclerosis, NMOSD = Neuromyelitis optica spectrum disorder, PT = prothrombin, PTT = partial thromboplastin time, RVVT = Russell's viper venom time, SS = Sjögren's syndrome.

**Keywords:** central nervous system sjögren's syndrome, cortical blindness, multiple sclerosis, neuromyelitis optica, neuromyelitis optica spectrum disorder, optic neuritis, plasma exchange, sjögren's syndrome

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## 1. Introduction

The demyelinating syndromes associated with Sjögren's syndrome (SS) have been proposed to recapitulate findings seen in multiple sclerosis (MS).<sup>[1]</sup> Cohort studies starting in the 1980s asserted that clinical and neuroimaging features of demyelinating disease in SS could therefore be difficult to discriminate from MS.<sup>[2]</sup> This legacy that MS may exist on a clinical and mechanistic spectrum with SS central nervous system disease is embedded in current SS activity indices, which describe demyelinating syndromes as "MS-type" disease.<sup>[3]</sup> However, with increasing recognition over the past decade that demyelinating syndromes are heterogeneous and encompass disorders other than MS, the demyelinating syndromes in SS have equivalently been recognized to include diverse presentations.<sup>[4]</sup>

In particular, the neuromyelitis optica spectrum disorder (NMOSD) is a distinct, immune-mediated, central nervous system (CNS) demyelinating syndrome with strikingly different clinical, autoantibody, and neuroimaging features from MS.<sup>[5]</sup> Recent studies have suggested that NMOSD may occur more commonly in SS than in MS.<sup>[6]</sup> NMOSD is associated with an antibody biomarker targeting aquaporin-4, expressed on CNS astrocytic foot processes, which is >95% specific for NMOSD versus MS.<sup>[4,5]</sup> Other characteristic features of NMOSD can include myelitis that spans at least 3 vertebral segments on magnetic resonance imaging (MRI, longitudinally extensive transverse myelitis [LETM]), and severe attacks of optic neuritis that may occupy >1/2 distance of optic nerves on MRI.

With this increasing recognition that SS patients may have a proclivity to be affected by NMOSD as opposed to MS, it is important to further consider recent studies suggesting a widening spectrum of NMOSD. For example, earlier iterations of NMOSD criteria emphasized its restriction primarily to cause optic neuritis and myelitis.<sup>[4]</sup> However, with increasing recognition that NMOSD can also more ubiquitously affect brain regions enriched in aquaporin-4 (AQP4), a more expansive panoply of clinical features can occur and reflects this diverse targeting of different CNS anatomic sites. Such clinical findings include nausea and vomiting (due to area postrema lesions), as well as narcolepsy and endocrinopathies (due to diencephalic lesions).<sup>[5]</sup>

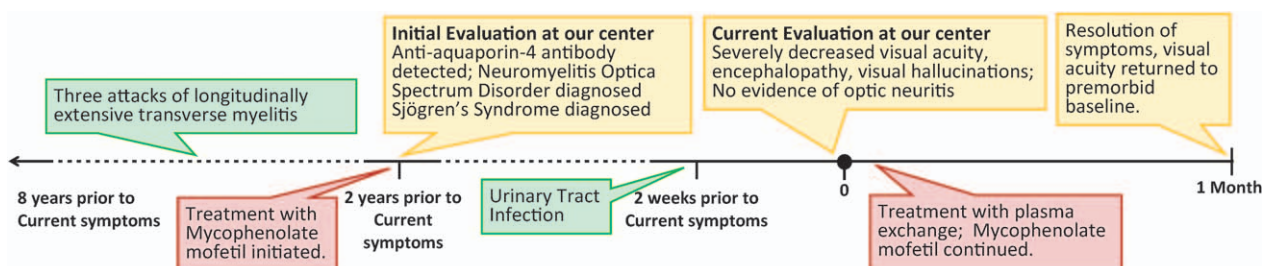
When encephalopathies occur in a SS patient with NMOSD, such encephalopathies may be attributed to underlying SS disease activity, or to infections potentiated by immunosuppressive therapy. However, the possibility that such encephalopathies may reflect more aggressive NMOSD activity, and warrant intensification rather than withdrawal of immunomodulatory therapy, may not be considered.

In this report, we describe the first example of a NMOSD patient surprisingly found to have severely decreased visual acuity due to cortical blindness and not optic neuritis. In this patient, other characteristic features of cortical blindness included visual hallucinations, encephalopathy, and contrast-enhancing occipital lobe lesions. All of these clinical and radiographic findings responded to plasma exchange (PLEX) therapy. Further discussions considering the management of such NMOSD presentations in SS patients are considered. The patient provided informed written consent to be included in this case report.

## 2. Case presentation

The patient is a 73-year old, right-handed Caucasian female, who presented with bilateral decreased visual acuity, encephalopathy, and episodes of visual hallucinations. The patient was initially referred to us 2 years ago, for evaluation of whether her demyelinating syndrome was occurring in the context of a rheumatic disease (see Fig. 1, timeline). In the 6 years before this initial evaluation, she experienced 3 attacks of recurrent LETM. Neuroimaging studies collectively demonstrated LETM from C7 to T5, and from T9 to the conus medullaris. With successive attacks, the patient cumulatively had loss of antigravity strength in the lower extremities, and was relegated to a wheelchair after the third attack. However, her outside physicians only treated each LETM attack with pulse dosages of intravenous methylprednisolone 1000 mg (for 3 to 5 successive days), but without starting any immunosuppressive therapies. The patient complained of dry eyes and dry mouth, and was therefore referred to our center for further evaluation. Upon our initial assessment, the patient stated that in retrospect, she had experienced symptoms of dry eyes and dry mouth for 5 years, but recently these symptoms had become more pronounced. Our evaluation confirmed the diagnosis of SS according to the 2016 ACR/EULAR classification criteria.<sup>[7]</sup> This was evidenced by objective testing revealing decreased tear production by Schirmer's test (<5 mm of tear production) (1 point), associated with the presence of both anti-Ro (SS-A) (3 points), and anti-La (SS-B) antibodies, which in our patient were qualitatively assessed by serum enzyme-linked immunosorbent assay (ELISA). According to these criteria, a score of  $\geq 4$  can establish the diagnosis of SS.

With regard to other serologies, antinuclear antibodies were present at a titer of 1:320 in a speckled pattern, with no rheumatoid factor, normal C3 (115 mg/dL) and C4 (14 mg/dL) levels. Assessment for antiphospholipid antibodies revealed no evidence of anticardiolipin IgM/IgG nor beta-2-glycoprotein IgM/IgG antibodies, and lupus anticoagulant was excluded on the basis of normal prothrombin time/partial thromboplastin



**Figure 1.** Timeline of disease, diagnostic features, and treatment with plasma exchange resulting in resolution of cortical blindness in a Sjögren syndrome patient with the neuromyelitis optica spectrum disorder.

time (PT/PTT) as well as no prolongation of Russell viper venom time (RVVT). The serum protein electrophoresis was suggestive of hypogammaglobulinemia with decreased gamma-globulin of 0.6 g/dL (normal 0.7–1.7 g/dL). IgG was mildly decreased at 649 mg/dL (normal 751–1560 mg/dL), IgM was mildly decreased at 33 mg/dL (normal 46–304 mg/dL), and IgA was 172 mg/dL (normal 82–453 mg/dL). The patient's mild decrease in IgG and IgM levels was not associated with pulmonary, sinonasal, or gastroenterological infections. In addition, we evaluated for and detected anti-AQP4 antibodies by a commercially available immunohistochemical assay.<sup>[4,5]</sup> Therefore, given recurrent episodes of LETM associated with anti-AQP4 antibodies, the patient satisfied criteria for NMOSD.<sup>[8]</sup>

On our initial neurological evaluation, we noted visual acuity of 20/60 in each eye, pupils were symmetric at 3 mm and reactive, there was no relative afferent pupillary defect, and fundoscopic examination was unremarkable. She was noted to have a spastic tetraparesis, with 5/5 strength assessed on manual research council scale<sup>[9]</sup> in the proximal upper extremities, 4/5 strength in the intrinsic hand muscles, 3/5 strength in hip flexors, and 1/5 strength in foot dorsiflexion. Reflexes were 3+ symmetrically in upper and lower extremities, with bilateral Babinski responses. There was decreased pinprick and temperature sensation in the lower extremity. She could only walk 5 yards with assistance of a walker and otherwise was relegated to a wheelchair. We elected to start treatment with mycophenolate mofetil titrated to 2000 mg (higher dosages not tolerated due to dyspepsia), which is among other immunosuppressive agents (i.e., rituximab and azathioprine) recommended to prevent relapses.<sup>[10–12]</sup>

This represented the patient's state of health until 2 years later, when her family brought her to our clinic with new symptoms of decreased visual acuity. Two weeks before this most recent evaluation, she suffered a urinary tract infection. She was admitted to an outside hospital, treated with antibiotics, and discharged. However, after discharge, her family reported episodes of visual hallucinations. The patient described seeing family members in the home who were not actually present, including some of whom were deceased. In addition, the patient complained of difficulty reading, and then seeing the television set. On our evaluation, she was only oriented to person, but not to place or time. She was only able to detect gross hand movements inches from her eyes but could not count fingers. However, she surprisingly did not have any findings supportive of optic neuritis. Her pupils were 3 mm, symmetrically constricting to light in both eyes, without findings of an afferent pupillary defect, and fundoscopic examination was normal. The remainder of her neurological examination revealed only unchanged findings of a spastic tetraparesis. She continued to have visual hallucinations of doctors and other family members who were not actually present in her room. She was therefore hospitalized for further evaluation.

MRI of the brain revealed disseminated pontine, periventricular, and occipital lobe lesions (Fig. 2). On axial FLAIR sequence (Fig. 2A), there was extensive T2 hyperintensity around the right ventricular atrium, which extended posteriorly to involve the juxta-cortical white matter of the right occipital lobe. There was also T2 hyperintensity affecting the pons (Fig. 2B). On T1 post-contrast sequences, there was enhancement in the periventricular regions (Fig. 2C,D), the occipital lobe (Fig. 2E), and along the anterior aspects of the pons (Fig. 2F). Given findings of severely decreased visual acuity with encephalopathy and hallucinations, an occipital lobe lesion, and no evidence of optic neuritis, the patient's decreased visual acuity was attributed

to cortical blindness. As described, cortical blindness is defined as the total or partial loss of vision in a normal-appearing eye (i.e., no optic neuritis), caused by damage to the brain's occipital cortex.<sup>[13,14]</sup>

Although most commonly associated with bilateral lesions in the occipital lobe, unilateral lesions have also been described.<sup>[13,14]</sup> The patient was treated with 5 consecutive days of 1000 mg methylprednisolone with no change in her neurological deficits. Therefore, as has been recommended for severe and steroid-refractory demyelinating diseases,<sup>[15,16]</sup> the patient was treated with PLEX. She received 5 courses of PLEX, given on alternate days. After the 5 courses of PLEX were completed, there was improvement in her mental status. She was alert and now oriented to place and time, and did not describe any further visual hallucinations. There was no immediate change in her visual acuity. She was discharged on a tapering course of prednisone, starting at 60 mg per day. The patient stated she wanted to continue therapy with mycophenolate mofetil.

She was discharged to a subacute rehabilitation center, and then re-evaluated 1 month later. There were again no further visual hallucinations or findings of an encephalopathy. In addition, the patient was now noted to have completely recovered her vision, back to her premorbid baseline of 20/60 in each eye, respectively. Repeat MRI studies are noted in Fig. 3. On axial FLAIR sequence, there was decreased hyperintensity around the right ventricular atrium, which no longer extended as far posteriorly to the juxta-cortical white matter of the right occipital lobe (Fig. 3A). On T1 post-contrast sequences, there was resolution of contrast enhancement in the right peri-atrial lesions, right occipital lobe, and pons (Fig. 3B–D).

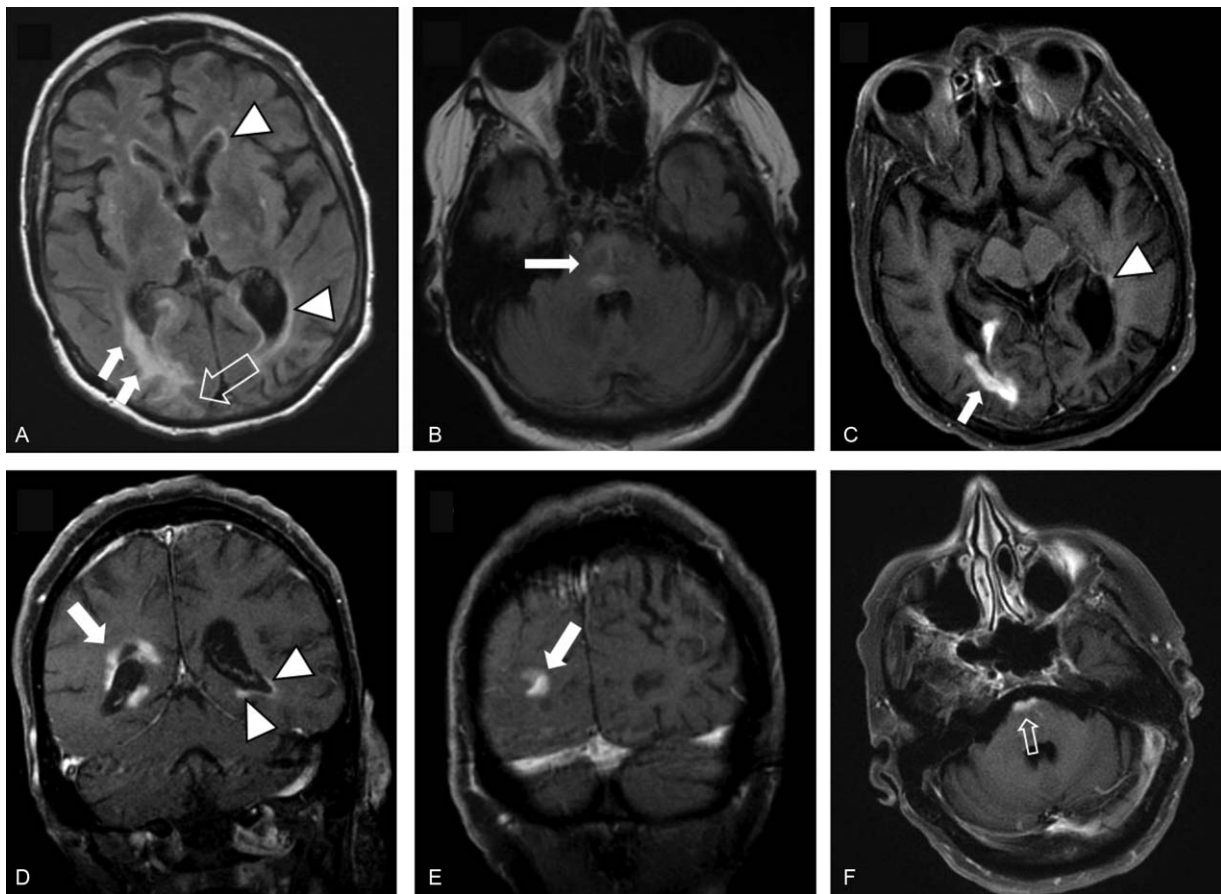
When followed over the subsequent year, the prednisone was tapered to off after 3 months, and there were no further episodes of demyelinating disease.

### 3. Discussion

We here describe the first case of severely decreased visual acuity in a NMOSD patient due to cortical blindness and not due to bilateral optic neuritis. Our patient lacked clinical findings of optic neuritis (i.e., with preserved pupillary constriction and no afferent pupillary defect), and instead presented with visual hallucinations, encephalopathy, and an occipital lobe lesion. Furthermore, an important feature is that our patient also presented with additional brain lesions, which have recently been recognized to be part of NMOSD criteria and reflecting anti-AQP4 antibody autoimmunity.<sup>[8]</sup> Further diagnostic, mechanistic, and therapeutic implications are considered below.

A challenging task when a SS patient presents with a demyelinating syndrome is to assess whether clinical syndromes and brain lesions are potentially consistent with NMOSD, or due to competing morbidities such as MS or CNS manifestations of SS disease. Over the 6 years before her initial evaluation at our center, she had 3 recurrent attacks of LETM. Upon our initial assessment, we evaluated for and detected the presence of anti-AQP4 antibodies. These collective manifestations would have been consistent with early conceptions of NMOSD (previously called NMO), as a syndrome causing optic neuritis and myelitis, but otherwise largely sparing the brain.<sup>[4]</sup> Under such earlier criteria, our patient's development of brain lesions would have been problematic and not consistent with NMOSD. Instead, to account for such brain lesions, a second and separate disorder such as CNS SS would need to be invoked. This unwieldy combination of 2 disorders would have clouded judgment about therapy.





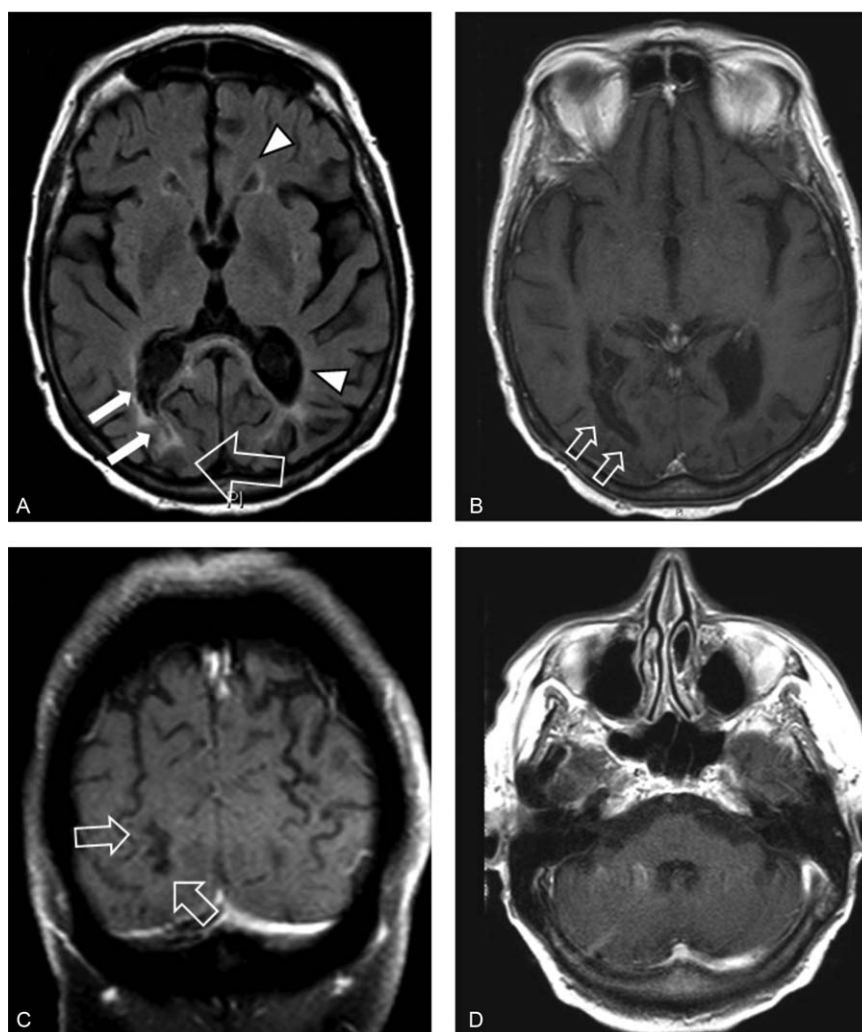
**Figure 2.** Magnetic resonance imaging (MRI) imaging of the brain before treatment with plasma exchange. (A) An axial FLAIR image demonstrates extensive T2 hyperintensity in the periventricular white-matter around the right ventricular atrium (arrows), and less prominently in other periventricular regions (arrowheads). The hyperintense signal changes extend posteriorly to involve the deep and juxta-cortical white matter of the right occipital lobe (open arrow). (B) Axial FLAIR image shows T2 hyperintensity affecting the pons (arrow). Axial (C) and coronal (D) T1 post-contrast sequences demonstrate periventricular contrast enhancement most pronounced surrounding not only the right atrial trigone of the lateral ventricle (arrow) but also in other periventricular regions (arrowheads). (E) Coronal T1 post-contrast enhanced image shows the enhancement in the right occipital lobe (arrow). (F) Axial T1 post-contrast sequences also show enhancement along the anterior aspect of the pons (open arrow).

However, studies have emphasized that brain lesions occur in the majority of NMOSD patients,<sup>[17]</sup> and suggest how NMOSD can accommodate brain lesions seen in our patient's most recent flare.<sup>[8]</sup> As seen in our patient, brainstem lesions are now included in NMOSD criteria,<sup>[8]</sup> and periventricular lesions infrequently occur and do not necessitate the diagnosis of MS. Whereas our patient's findings of cortical blindness have not been described as stemming from an occipital lobe lesion in NMOSD, cortical lesions associated with seizures and confusion have been reported.<sup>[18]</sup> These findings suggest that cortical blindness and occipital lobe lesions are consistent with this widening spectrum of NMOSD. In fact, given that anti-AQP4 antibodies are ~100% specific for NMOSD versus MS,<sup>[5]</sup> the diagnosis of MS in our patient can be excluded. Therefore, the patient's initial presentation (recurrent LETM) and current presentation are all consistent with a singular diagnosis of NMOSD, and does not necessitate invoking a second autoimmune disease.

Our patient's brain MRI had other findings suggesting NMOSD and associated anti-AQP4 antibody autoimmunity as a unifying syndrome for her CNS disease. Brain regions that upregulate AQP4 autoantigen may be vulnerable to damage by anti-AQP4 antibodies, especially in situations when there is increased permeability of the blood-brain barrier.<sup>[5]</sup> In our

patient, given that infection is known to breach the blood-brain barrier, the antecedent episode of a urinary tract infection likely potentiated anti-AQP4 antibody autoimmunity. In addition, a notable finding was that there was joint enhancement of the occipital lobe lesion with brainstem and periventricular lesions. Such synchronous enhancement further attests to a unifying diagnosis of NMOSD, and again illustrates how invoking a secondary disorder (i.e. MS or SS) is not necessary.

Recognition that NMOSD was coincidental to her SS was instrumental in the decision to treat our patient with PLEX. For example, PLEX is used in severe, steroid-unresponsive attacks of demyelinating disease,<sup>[15,16]</sup> but is otherwise not used for extraglandular manifestations of SS. Our patient initially failed therapy with corticosteroids, but had a substantial response to PLEX therapy. She was no longer blind, did not have further visual hallucinations, had resolution of encephalopathy, and strikingly also had resolution of contrast-enhancing lesions in the brainstem, periventricular regions, and occipital lobe. Therefore, knowledge that NMOSD and SS are coincidental can reinforce the need of using PLEX when SS patients experience severe flares of demyelinating attacks. These MRI findings also complement other immunological studies suggesting NMOSD as being entirely coincidental to SS.<sup>[6,19–21]</sup> Such studies identified anti-



**Figure 3.** Magnetic resonance imaging (MRI) of the brain performed after treatment with plasma exchange. (A) Axial FLAIR sequences demonstrate decreased T2 hyperintensity of the peri-atrial white matter surrounding the right ventricle (arrows), as well as other periventricular regions (arrowheads). There is also decreased T2 hyperintensity of the hemispheric lesion extending from the right peri-atrial region into the occipital lobe (open arrow). (B) Axial T1 post-contrast sequence shows resolution of contrast enhancement affecting the right peri-atrial lesions (open arrows). (C) Coronal T1 post-contrast sequence shows resolution of contrast enhancement affecting the right occipital lobe (open arrows). (D) In addition, on axial T1 post-contrast sequence, no contrast enhancement is noted in the pons.

AQP4 antibodies exclusively in SS patients with NMOSD, not in any SS non-NMOSD patients, and with such 100% syndrome specificity indicating that our patient's NMOSD was not a CNS manifestation of SS.<sup>[6,19–21]</sup>

In summary, we have provided the first example of a patient with NMOSD who had severely decreased visual acuity due to cortical blindness and not bilateral optic neuritis. Our patient's brain MRI findings emphasize how NMOSD is an expansive syndrome not limited to optic neuritis and myelitis. Therefore, a SS patient with steroid-refractory NMOSD should be treated with PLEX, similar to a NMOSD patient without an accompanying autoimmune disease.

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