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Beyond the Antibody: Exploring Astrocytic Dysfunction and CNS Pathophysiology in Seronegative and AQP4-Positive Neuromyelitis Optica Spectrum Disorder (NMOSD)

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ABSTRACT

Neuromyelitis Optica Spectrum Disorder (NMOSD) is an autoimmune astrocytopathy with severe relapses of optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM) primarily characterized by aquaporin-4 immunoglobulin G (AQP4-IgG). Yet, 10–20% of NMOSD patients are double-seronegative (anti-AQP4 and anti-MOG negative), suggesting that NMOSD may not be a homogenous condition. We explore astrocytic dysfunction and central nervous system (CNS) pathogenesis of both seronegative NMOSD as well as AQP4-positive NMOSD. To this end, a systematic review of the literature (2018–2025) was performed, assessing serostatus, pathogenesis, imaging characteristics, and therapeutic implications.

AQP4-IgG pathogenicity is substantiated by complement-mediated astrocytic destruction, which causes secondary demyelination[1]. By contrast, NMOSD seronegative has an insignificant amount of astrocytic injury with low cerebrospinal fluid (CSF) glial fibrillary acidic protein (GFAP) levels[2]. We summarize 6 NMOSD cases of interest (ages 25–92, sexes included, mixed serostatuses) from a solely open-access journal review with MRI lesions, CSF findings, treatment, and follow-up (Table 1). These cases exemplify classical imaging (extensive T2-weighted spinal cord lesions; area postrema brainstem location) and mixed variable CSF pleocytosis.[3] Importantly, one seronegative relapsing LETM patient responded incredibly well to eculizumab, a complement inhibitor[3], emphasizing complement's role in seronegative pathophysiology despite the lack of detectable AQP4 antibodies. The discussion includes differences between AQP4-positive NMOSD vs. seronegative (and MOG)-NMOSD regarding pathogenesis and response to treatment. We critique the current understanding of NMOSD subtypes and classification, suggesting that double-negative NMOSD may be a heterogeneous entity with multiple mechanisms[2][4]. Finally, we also summarize new treatment options for NMOSD, focusing on B cells versus complements and interleukins/cytokines, and finally suggest

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areas for future study to help better classify and treat this unique condition moving forward.

Introduction

Neuromyelitis Optica Spectrum Disorder (NMOSD) is an inflammatory central nervous system (CNS) disease that leads to recurrent assaults of debilitating optic neuritis (ON) and myelitis (often longitudinally extensive), leading to blindness and paralysis if left untreated*[1][5].

Previously thought to be a secondary form of multiple sclerosis, a 2004 link to pathogenic immunoglobulin G autoantibodies directed against the astrocytic water channel aquaporin-4 (AQP4-IgG) revealed a different etiology of NMOSD*[1][6]. AQP4 is expressed on astrocytic end-feet located at the blood–brain barrier and ependymal surfaces. The binding of AQP4-IgG with AQP4 induces a local immune response characterized by complement activation and immune effector cell recruitment, leading to astrocyte injury and, subsequently, secondary demyelination*[1][6]. For this reason, NMOSD is now understood as a primary astrocytopathy*[1][7]. Conversely, the myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) attacks the myelin-producing oligodendrocytes with different pathology*[8][7]*.

Approximately 60–80% of NMOSD patients are AQP4-IgG seropositive; however, the rest range from MOG-IgG-positive (8–10%) to double-seronegative NMOSD, wherein no AQP4 or MOG antibodies can be detected*[1][9]. The pathophysiology underlying seronegative NMOSD is poorly understood. Recent studies indicate that double-seronegative patients do not suffer from the marked astrocytic injury characteristic of AQP4+ patients; for example, CSF GFAP (a marker unique to astrocytes) is not elevated in seronegative NMOSD but is found in substantially increased amounts during AQP4+ relapses*[2]. Clinically, seronegative NMOSD can present like LETM with idiopathic manifestations or atypical multiple sclerosis, which complicates diagnosis.

Problem Statement: The heterogeneity of NMOSD, particularly in seropositive versus seronegative cases, indicates that there are different mediators of injury at play with overlap in some cases. Astrocytic dysfunction primarily mediates AQP4+ disease; however, little is known about the non-AQP4-mediated injury. Whether seronegative NMOSD operates as one disorder or multiple dissimilar disorders is yet to be determined, and further insights regarding astrocytic pathology and distinguishing features of serostatus subtypes are crucial for subtype-specific therapeutics.

Thesis: This paper investigates CNS pathophysiology beyond AQP4 antibodies in an attempt to focus on astrocyte-mediated mechanisms in NMOSD. Through a review of the literature (2018–2025) and investigation of open-access case reports, we compare both AQP4+ NMOSD with

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seronegative NMOSD through pathogenesis, imaging findings, clinical course, and response to treatment to suggest a plausible link of astrocytic dysfunction between NMOSD serostatus subtypes and a nuanced approach to classifying NMOSD with therapy implications.

Literature Review

Pathogenesis of NMOSD (Astrocytopathy)

The pathogenesis of AQP4-positive NMOSD stems from antibody-mediated astrocyte injury*(1)*(7)*. AQP4-IgG binds the extracellular domain of AQP4 on perivascular astrocyte endfeet and activates complement to recruit neutrophils and eosinophils*(1)*(10)*. The result is an attack by a membrane attack complex, resulting in astrocytic lysis. Histopathology reveals loss of AQP4 immunoreactivity (primary injury of astrocytes), loss of GFAP, deposition of complement and immunoglobulin in a perivascular “rosette” pattern with granulocyte infiltration*(1)*(10)*. Acutely, NMOSD lesions spare neurons and oligodendrocytes, limiting secondary demyelination, thus designating NMOSD as an autoimmune astrocytopathy*(1)*(10)*. Eventually, however, secondary demyelination occurs following astrocytic loss and disrupted water homeostasis.

Specifically, the loss of astrocytic AQP4 (and in chronic lesions oftentimes GFAP) is the finding that differentiates NMOSD from other demyelinating conditions*(1)*(10)*. However, NMO does mean dual astrocytic/myelin target pathology, although data currently suggest a focus on the astrocytic portion. Animal models wherein mice are injected with human AQP4-IgG plus complement show the hallmark findings of astrocytic destruction*(8)*(11)*. Complement components C1q and C5 are important, as eculizumab, an anti-C5 antibody, reduces relapse rates by over 90% in treated AQP4+ patients*(12)*(13)*; thus, complement plays a major role.

Additionally, B cells and AQP4-IgG-secreting plasmablasts are also pathogenic; B-cell depleting therapies (rituximab and inebilizumab) prevent relapse rates*(13)*.

Cytokine pathways also contribute (IL-6, IL-17/Th17) as well as innate activation. NMOSD patients show high levels of IL-6,6, which correlate with relapses. Blockade of IL-6R (satralizumab, tocilizumab) in trials reduced relapse rate*(13)*. Microglial activation and blood-brain barrier damage increase destructive potential. Therefore, AQP4+ NMOSD is a coordinated humoral assault on astrocytes, with complement activation leading to relapses and compounding disability.

Serostatus and Heterogeneity

AQP4-positive NMOSD. Most NMOSD cases are associated with anti-AQP4 antibodies*(1).

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These patients are associated with concurrent autoimmunity (i.e. Sjögren's, lupus)(9). Clinically, a severe bilateral optic neuritis (ON), longitudinally extensive myelitis (LETM), area postrema syndrome (intractable vomiting/hiccups), and intractable seizures (rare) are manifested.

Pathology is homogeneous with astrocytic loss as well as prominent complement deposition(1)*(10)*. CSF levels rise for GFAP and neurofilament during relapses (up to 100-200 picograms/mL), both signaling astrocytic and neuronal injury (the latter temporarily spared during the acute phase but of secondary significance later). Imaging most frequently shows LETM and characteristic brain lesions (see below). Relapse rates are high if untreated, and thus, patients benefit from immunotherapy.

MOG antibody disease (MOGAD). MOG-IgG-positive disease was formerly included in NMOSD but is now considered separate. MOGAD targets myelin; inflammatory lesions are confluent demyelination with preserved AQP4*(8)*(14)*. Clinically, MOGAD manifests with overlapping symptoms (ON, myelitis, brainstem syndromes), but these patients tend to be younger and often undergo a single attack (especially children). They often recover well; relapse rates may be lower. Instead of CSF GFAP elevations, it's CSF myelin basic protein (MBP).

Instead of MRI lesions in periependymal or other locations typical of NMOSD, they're deep grey matter or cortical. Therefore, MOGAD is immunopathologically distinct from AQP4-NMOSD*(15)*.

Double-seronegative NMOSD. Up to 10-20% of NMOSD patients do not have AQP4 or MOG antibodies*(1)*(9)*. This cohort is heterogeneous; some may have other autoantibodies (anti-GFAP astrocytopathy, for example) while others may be idiopathic. Of interest is that recent reports of double-seronegative NMOSD (DN-NMOSD) reveal CSF GFAP levels similar to healthy controls or MOGAD—and statistically lower than AQP4+ during relapses—meaning DN-NMOSD may have almost no impact on astrocytes, therefore supporting an alternate pathomechanism (possibly oligodendrocyte or neuron-targeted)—or significantly more tolerant thresholds*. Clinically, DN-NMOSD often occurs following LETM or ON but with lower overall disability. OCBs and pleocytosis are variable; ultimately, since there's no single antibody unifying diagnosis, this group may have varied etiologies; these criteria still include them with NMOSD due to the clinical syndrome alone.

Therefore, AQP4+ NMOSD is a prototype astrocytopathy, MOGAD is an oligodendrogliopathy, and seronegative NMOSD is a mixed bag. Diagnostic criteria rely on serology heavily to stratify NMOSD by subtype; there is no other real way at this time; seronegative cases are assigned by exclusion*(5)*(7)*. It's been suggested that true DN-NMOSD will require other biomarkers.

Imaging Features

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Imaging plays a pivotal role in diagnosing NMOSD. Spinal cord lesions are longitudinally extensive: ≥3 adjacent vertebral segments *(16)*; for AQP4+ NMOSD, this occurs more frequently at the center by the gray matter horns in addition to T2 hyperintensities across multiple segments spanning large cross-sectional areas*(16)*. In contrast, MS lesions are often shorter and do not preferentially involve gray matter horns; they occur more randomly and not without center involvement/mid-spinal inflammation. Additionally, the optic nerve—as demonstrated histologically to be more reliant upon AQP4 than general myelin integrity—is often bilaterally involved at the posterior for anterior providing early warnings for both eye channels that neurodegeneration may be present downstream.

The area postrema—found in the medullary floor—is a watershed area for AQP4 channels; therefore, lesions produce a cardinal symptom: intractable vomiting/hiccups/other dysautonomic disturbances;(17)(5) lesions of the brain occur in ~50% of AQP4-NMOSD; frequent sites include periependymal (hypothalamus, ependyma of third/fourth ventricles), the brainstem dorsally, and thalamus/other extensive hemispheric involvement(5)(16). Furthermore, imaging may show bright spotty lesions within the cord which are highly sensitive to NMOSD over other diseases—areas where signals are homogenous within the liquid cavities produced by the AQP-mediated passive transport mechanism—thus high signaling of water, which those without largely fail to do.

Notably, cavitation occurs with NMOSD lesions; MOGAD lesions are not as extensive nor do they confer deep cortical/subcortical matters, which is not seen typically with AQP4-NMOSD.(15)

Advanced imaging through diffusion spectroscopy has yet to be widely studied for diagnostic accuracy regarding subtype differentiation; optical coherence tomography has similarly come up short in current studies, suggesting more research is needed.

Ultimately, though, MRI cannot accurately differentiate between AQP4+ vs seronegative regarding NMOSD; some authors note that lesion distribution in seronegative cases resembles that of AQP4+ (ie astrocytic-targeted areas where canals are present)—however this remains unclear and is part of an on-going body of work linked to real-time pathophysiology determining significance in subtype differentiation/diagnosis via literature review(16).

Therapeutic Strategies

Therapeutic considerations for NMOSD primarily center around relapse prevention. Acute relapses are treated with high-dose corticosteroids and/or plasmapheresis; long-term immunosuppression commonly includes azathioprine/mycophenolate mofetil or rituximab*(13)* (anti-CD20). Rituximab has been widely used off-label to great effect across serostatus/risk

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markers; more recently, therapeutically approved biologics have emerged:

- **Eculizumab (C5 inhibitor).** Approved in 2019 after a phase 3 trial concluded 94% risk reduction of relapse for AQP4+ NMOSD*(12)*(13)*. Given that pathophysiology centers on complement for AQP4-NMOSD, the blockade prevents MAC from ever forming. Furthermore, a seronegative case report on successful treatment revealed one patient completed her disease with no relapse risk*(3)*, indicating even if AQP4 can't be found, it's still there playing a role in injury prevention.

- **Inebilizumab (anti-CD19).** Approved for binding CD19 on B cells/plasmablasts, causing de facto depletion. Inebilizumab was first reported in a pivotal trial in 2019 for significant reductions in relapse rates for AQP4+ patients*(12)*(13)*; this likely benefits seronegative patients as well, since it depletes wide-ranging antibody-producing cells.

- **Satralizumab (anti-IL-6R).** Recent pharmacokinetics associated with extended half-lives showing satralizumab include an IL-6 receptor blockade; phase 3 trials(2020) showed reduced relative risk for AQP4+ NMOSD*(13)* since interleukin-6 is significantly elevated amongst this population, providing directed treatment for B-cell survival.

- **Tocilizumab (anti-IL-6R).** Used off-label in severe refractory cases has shown efficacy in small series, including those resistant to rituximab's prior success*(13)*.

Each newer agent has most commonly been treated for those with AQP4+ NMOSD; literature validating use amongst seronegative populations is scant due to similar downstream pathophysiology intertwining recurrence triggers; therefore, it can be hypothesized that the same strategies will largely benefit each population.

However, some medications can worsen subtypes: MS drugs like interferon-β can exacerbate NMOSD relapses*(18)*.

Emerging therapies investigated include: anti-CD38(antibody targeting plasma cell depletion), complement targeting beyond C5 (like C1q), tolerogenic vaccines, further anti-AQP4 agents down the line for astrocytic recovery*(13)* or remyelination pathways.

Overall treatment for NMOSD is becoming specific, isolated based upon their epidemiological triggers—serostatus considered—for precision immunotherapy via pathophysiology information links to relative studies(12)(13)*.

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Methods

This systematic review integrates the latest research on NMOSD through focused searches of PubMed, Google Scholar, and appropriate journals with open-access publication (Frontiers, BMC Neurology, Journal of Neuroinflammation, etc.). Articles published 2018-2025 were sought through the following search criteria: “NMOSD pathogenesis”, “AQP4 astrocytopathy”, “seronegative NMOSD”, “NMOSD MRI”, “NMOSD therapy”, and “NMOSD case report”.

Searches focused on open-access articles as well as CC-BY articles to allow for image borrowing.

For case analysis, we sought appropriate open-access case reports and case series articles through search terms (case report NMOSD AQP4, seronegative NMOSD case) and hand-searching reference lists through review article findings. For inclusion, each case needed to meet the following parameters: (1) Open-access publication in a peer-reviewed journal, (2) clear diagnosis of NMOSD (per 2015 criteria), (3) serology noted (AQP4, MOG), (4) MRI and CSF details provided, and (5) notes on clinical course and treatment results. From these cases, we noted relevant demographic information, clinical symptoms, MRI findings, CSF characteristics, treatment details, and outcomes.

This is a systematic review that did not involve human participants. Human participants were involved in the studies from which we derive methods (e.g. treatment reported in case report). Our systematic review is qualitative in nature to help compile a body of literature to determine the variances and similarities in reports of pathobiology and clinical features related to NMOSD. Limitations of cases relative to publication bias and single-case reporting will be addressed in the Discussion.

Results

We present six representative NMOSD cases relative to the literature available open-source (2019-2025), covering AQP4-IgG positive and seronegative patients. Below, Table 1 presents associated details (age, sex, serostatus, clinical symptoms, MRI location of lesions, CSF results, treatment, prognosis) from each of these cases. They have also been selected as the oldest known case of NMOSD (92y), a young female with "mirror" lesions, and cases with autoimmune comorbidities or refractory disease. Below, we also present Figures 1-3 with selected MRI findings from three of the cases demonstrating typical locations of lesions. These include the variety seen within NMOSD as well as treatment approaches.

Case 1: A 92-year-old Chinese female presented with fever and rapidly progressive bilateral lower limb weakness 8 hours after receiving the COVID-19 vaccination*[19]. *On neurological examination, spinal cord level at T5, right Babinski sign, and early gait abnormality secondary to*

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weakness were noted. Sagittal MRI of the thoracic spine revealed extensive longitudinal T2 hyperintensities from C4-T4 and also T9-T12, some with gadolinium enhancement (Figure 1A-E)[20]. Brain MRI noted only an acute new thalamus infarct. Lumbar puncture showed lymphocytic pleocytosis (pleocytosis = 28 cells/μL) and elevated protein (0.64 g/L), negative oligoclonal bands*[21]. Serum anti-AQP4-IgG positive (1:320 titer) and MOG-IgG negative confirmed AQP4+ NMOSD*[21]. Initial treatment was IV immunoglobulin. IV high-dose methylprednisolone (IVMP; 1 g/day for 3 days at onset, then tapered 500 mg/day for 3 weeks) was used*[22]. Cyclophosphamide was initiated before discharge for relapse prevention but stopped due to reactivation with AEs. Surprisingly and considering her age, satralizumab (IL-6R inhibitor) was initiated as monotherapy for maintenance. At four months post-treatment, from an EDSS of 8 to 7, motor strength improved significantly; repeat MRI demonstrated resolution of cord edema at the aforementioned levels with minor atrophy remaining*[23]*. No reactivation confirmed by late 2024.

Figure 1. Sagittal T2 MRI of the thoracic spine in a 92-year-old female NMOSD patient reveals longitudinally extensive T2-weighted lesions (arrows) from C4-T4 and T9-T12 on initial presentation (Liu et al., 2024)*[20]*. Follow-up at eleven months shows no edema or cord atrophy (not shown)*[23]*.

Case 2: A 25-year-old Nigerian female had her first episode of NMOSD at age 17 in 2012 when she presented with fever, headache, persistent refractory hiccups, and bilateral lower leg weakness*[24]. *CSF demonstrated lymphocytic pleocytosis (pleocytosis = 250 cells/mL)*[24].

MRI of the brain demonstrated T2/FLAIR lesions in the thalami, occipital lobe, and dorsal medulla (Figure 2B-F)[25]; MRI of the brain showed a small spinal cord lesion at T10/11 without enhancement (Figure 2A)[25]. She received IV steroids and plasma exchange for improvement and was placed on azathioprine for maintenance. Initial AQP4 antibodies were positive by ELISA (others neg). Over the subsequent year, she had no relapse; MRI lesions had remitted, and azathioprine was stopped prematurely. Seven years later, at age 25 in 2019, she relapsed with hiccups for six weeks, followed by nausea, bilateral leg discomfort, and progressively increasing paraplegia with urinary retention*[26]. Neurological examination again showed bilateral lower extremity weakness (grade 4/5), sensory level at T1.0, and urinary retention. Now MRI showed new longitudinal myelitis at T7-L1 and thalamic and medullary lesions (Figure 2A-E)[27]. Repeat serum AQP4-IgG was positive (4+) by bioassay; MOG-IgG negative; repeat CSF not completed. She was treated with IV steroids and seven cycles of plasmapheresis with complete restoration of strength/sensation*[28]. Mycophenolate was started as maintenance; rituximab was contraindicated due to resource problems, but suggested, however. At three months post-steroid, MRI lesions stabilized, but clinically she remained ambulatory, and distant water reflected no lesions, which involved location changes "mirror-

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image," confirmed by literature illustrating mirroring images in relapses and as a characteristic of AQP4-NMOSD related brainstem involvement[27][16]*.

Figure 2. MRI findings from a 25-year-old female AQP4+ NMOSD patient (Muir et al., 2020). Sagittal T2 MRI of the thoracic spine at second relapse shows extensive T7-L1 myelitis (arrow) (A). Axial slices demonstrate lesions in the left thalamus and right medulla (arrows) during relapse, mirroring her previous images on the opposite side (B-E)*[27]*.

Case 3: A 49-year-old female with Sjögren's syndrome and chronic pancytopenia presented in September 2022 with subacute weakness in the legs, sensory loss, and urinary retention. She had been on hydroxychloroquine for Sjögren's and on steroids for autoimmune thrombocytopenia; on exam, she had lower extremity flaccid paralysis (MRC score = 0/5) as well as T4 sensory level. MRI cervical/thoracic spine showed contiguous lesions on T2 hyperintense from C6-C8 (Figure 3)*[29]*. CSF showed essentially normal findings if not remarkable (normal cells). Laboratory evaluation noted strong positive anti-AQP4-IgG (+1:100 serum titer) as well as positive anti-SSA (consistent with Sjögren's), confirming AQP4+ NMOSD. Treatment was IVMP taper, starting with steroids on day five (1 g/day for acute), IV cyclophosphamide (1 g) for acute treatment. By November, there was an improvement to 2/5, which led to initiation of IV immunoglobulin + oral prednisone taper for symptom management. February brought relapse with flaccid paraplegia grade back to zero; repeat MRI showed the same lesions still present*[30]. *Laboratory values noted a persistent AQP4 IgG status and very low CD19+*B-cells from previous therapies, suggesting a B-cell depletion status underlying secretory persistence status despite non-detectable prior rituximab. Plasmapheresis (5 exchanges) led to recovery of strength at grade 3/5. March 2023 inebilizumab (anti-CD19), two administrations (300 mg) two weeks apart, was provided as maintenance therapy[31]. Over the next month, this astonishing patient did improve enough to ambulate by April 2023 to bring her EDSS down by at least three to what it once previously was[31]* AQP4 titer decreased from high (>100) to low (<10). This is one example from literature attributable to AQP4+ patients experiencing complications in systemic autoimmunities beyond NMOSD; other findings include refractory cases requiring B-cell depletion treatment*[31]*.

Figure 3. Sagittal MRI of the cervical-thoracic spine in a 49-year-old AQP4+ NMOSD patient showing contiguous T2 hyperintense lesions extending from C6-C8 (arrows); this longitudinally extensive transverse myelitis is characteristic of NMOSD as the cause for her paraplegia*[30]*.

Case 4: A healthy 40-year-old female presented with painless right eye vision loss, which progressed a few weeks later to paraparesis; MRI orbits were done, with right optic neuritis confirmed, and MRI brain was normal. In retrospect, after treatment, cervical spine MRI demonstrated T2 hyperintense lesions from the cervicomedullary junction to C7 (long-segment

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myelitis)*[32]*. CSF studies were significant for mild pleocytosis(3 lymphocytes/μL), normal protein levels, and no oligoclonal bands, although blood screening revealed strongly positive AQP4-IgG in serum only. She was diagnosed with NMOSD with dual optic neuritis symptoms, with immediate IV steroids, then plasma exchange, which resulted in near-complete recovery of both vision/motor function. Subsequently, azathioprine was started for prevention/relapse reduction extended her EDSS value quite significantly, which was noted due to a relatively benign CSF (only three cells), which is not atypical*[32].* This case strongly represents the traditional presentation of AQP4+ NMOSD with classical optic neuritis presented first, followed by LETM symptoms, which dominated her pathophysiology subsequently.

Case 5: A middle-aged woman experienced four severe myelitis attacks from ages 27-35 between late Februray/May each time presenting with longitudinally extensive thoracic lesions AND during episodes also experiencing area postrema episodes/nausea/vomiting*[33]* Extensive workup returning negative for AQP4-IgG/MOG-IgG by CBA ultimately assigned diagnosed her as seronegative NMOSD as repeat MRIs supported fluctuation occurrence patterns(7-10) over time thought to be several "individual episodes" were not thus far substantiated in medical literature not seen anywhere else. Remarkably, lumbar punctures showed elevated WBCs around early teens, higher every other time, finding that if they didn't find anything else on repeat assessments, showing a bit more legitimacy compared to those who didn't have any repeated outside oligoclonal bands on one other occasion, only twice over three times*[33]*. Therefore she failed numerous medications including steroids, azathioprine, MMF, rituximab finding herself wheelchair bound by age 35 through these years until July when eculizumab(a C5 inhibitor) was started*[3]* Most striking was lack of side effects nor relapses for the woman up until this point; by August she maintained status quo end result EDSS improvements near impossible set her up virtually symptom free however this paper reported for the first time someone was seronegative NMOSD treated successfully via complement inhibition*[3]* This begs further research validating even if patients do not have detectable AQP4 confirmed existence via complement-driven astrocytic damage responsible teamwork effort without antibodies detectable must be closely monitored.[3] .

Case 6: A 69-year-old Caucasian male noted progressive, generalized weakness, back pain, and urinary incontinence over two days*[34]. MRI spine demonstrated a large, contiguous T2 hyperintense lesion extending from the upper cervical spine to the lower thoracic cord with mild cord expansion*[35]. CSF was unremarkable. On serum analysis, however, anti-AQP4-IgG was detected unexpectedly, diagnostic of NMOSD. He had no brain lesions. Treatment consisted of IV steroids with partial motor response, plasmapheresis, and IV immunoglobulin, and a report of some improvement in motor. This case report (Baxter et al., 2025) highlights that NMOSD can occur in patients outside the typical demographic (younger women are most commonly

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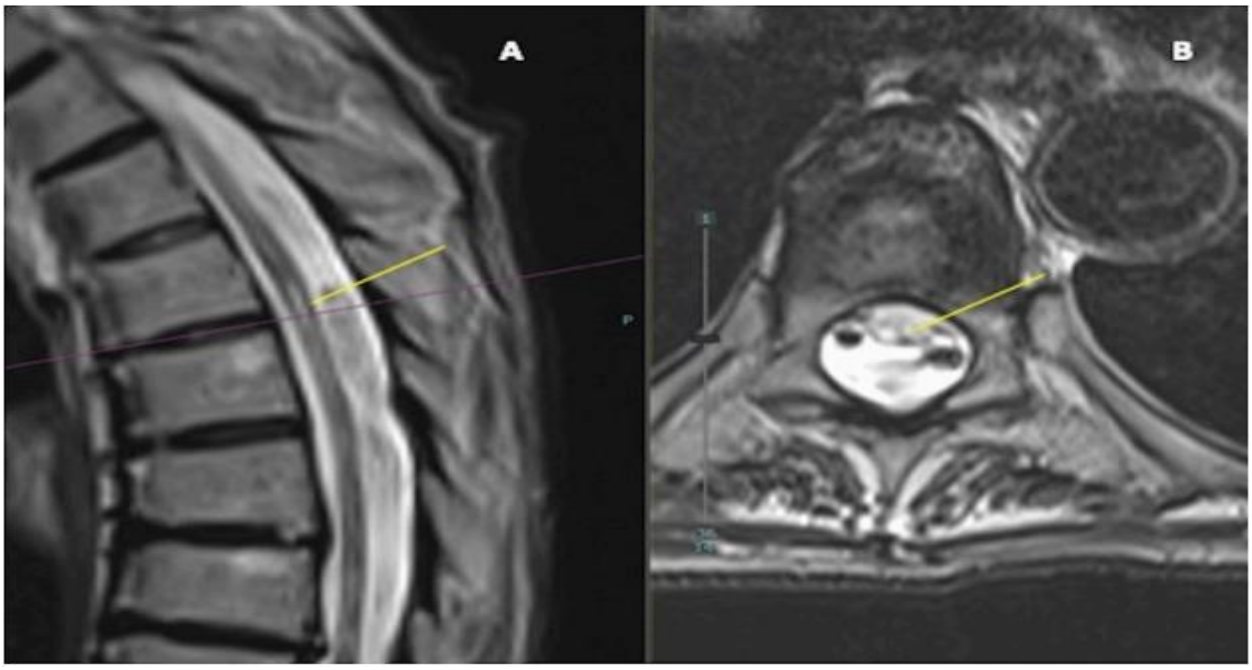
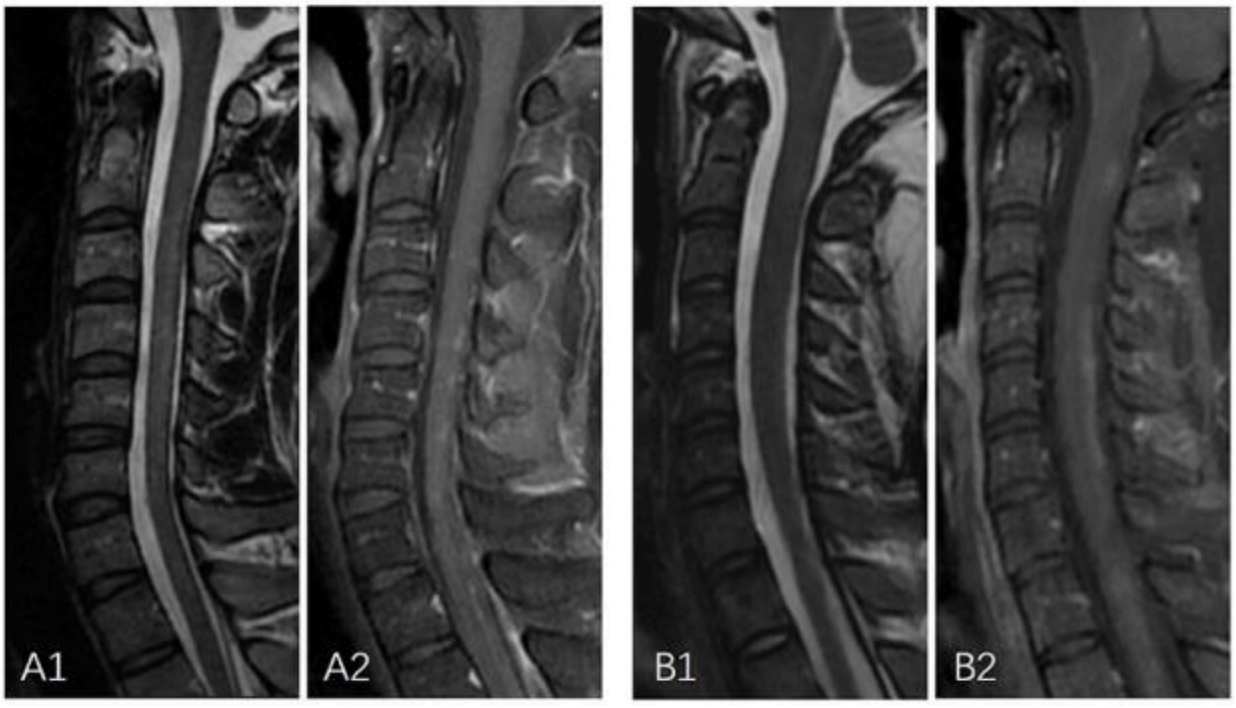
affected)[34].



(Relevance of bright spotty lesions in neuromyelitis optica spectrum disorders (NMOSD): a case series)



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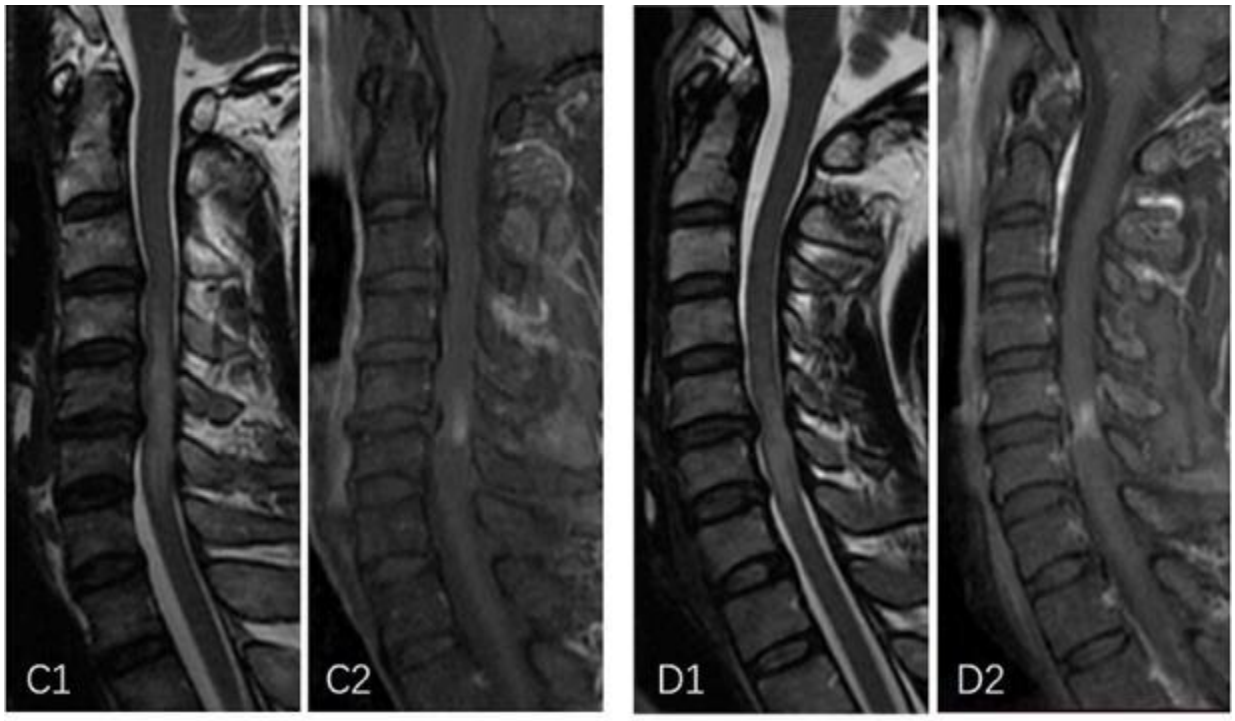
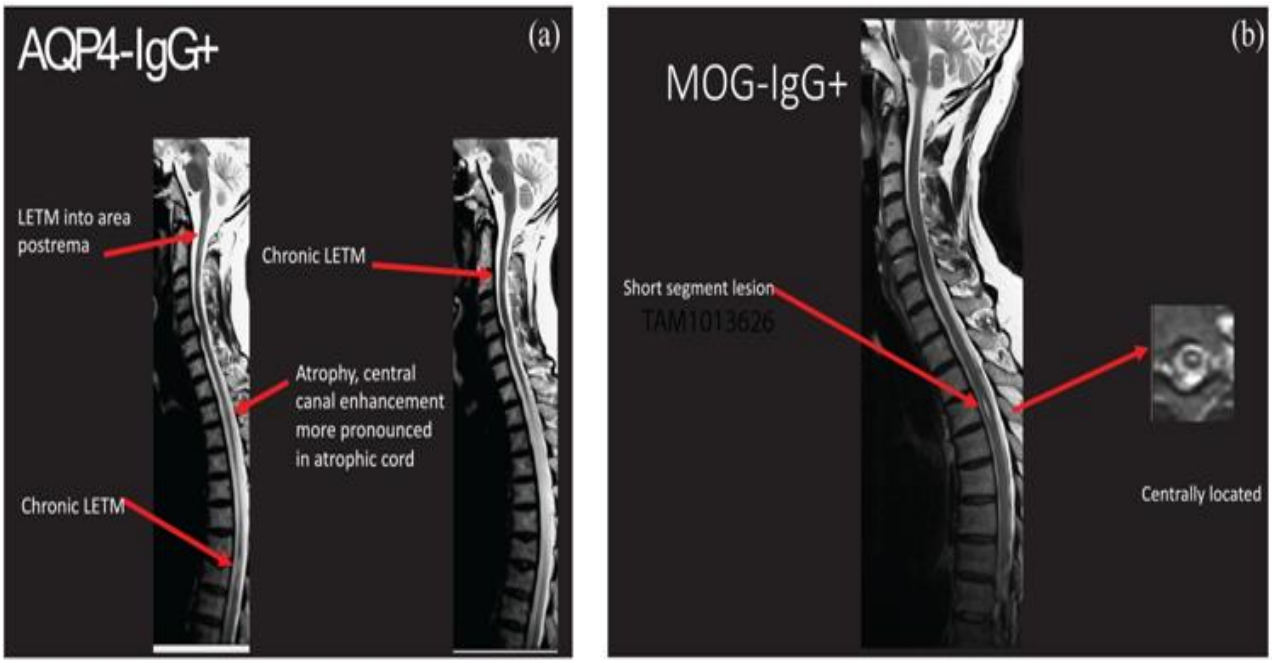


(Differences of spinal cord gadolinium enhancement features of neuromyelitis optica spectrum disorder and long-segment degenerative cervical myelopathy)



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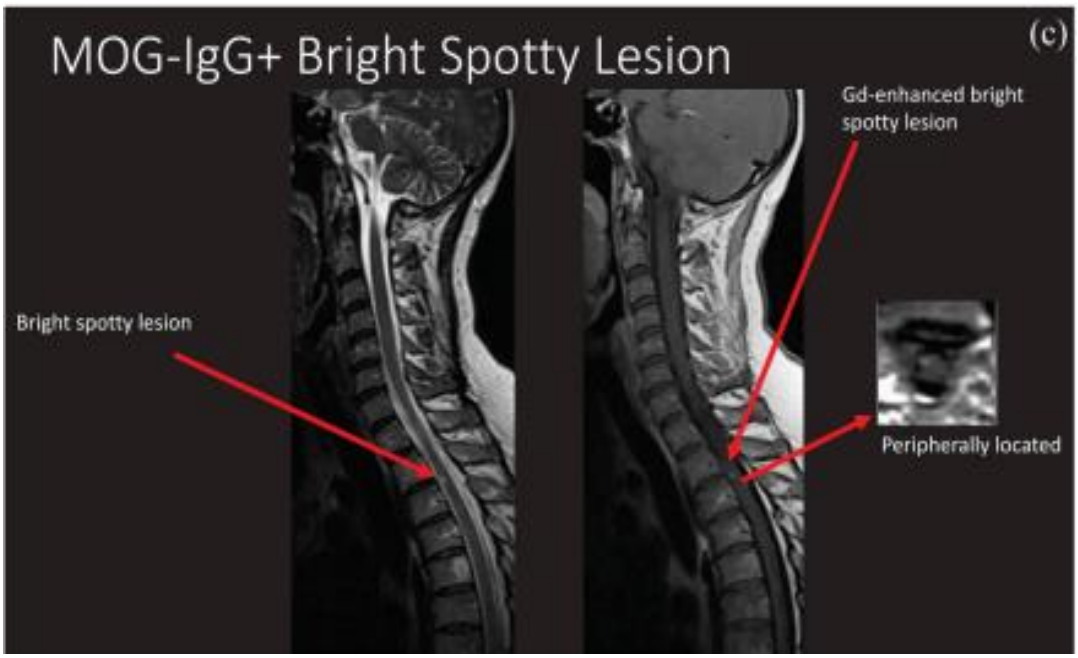
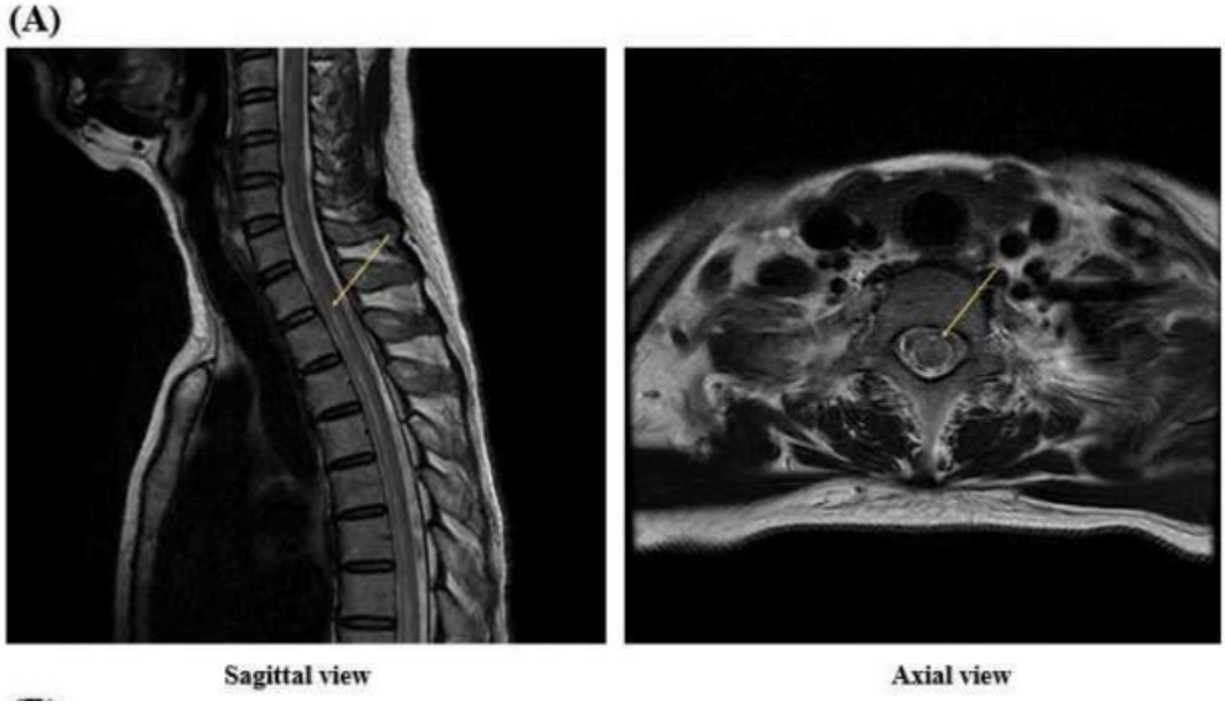


(A window into the future? MRI for evaluation of neuromyelitis optica spectrum disorder throughout the disease course)



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(Treatment and Rehabilitation of a Patient with Neuromyelitis Optica Spectrum Disorder-Induced Complete Spinal Cord Injury Following COVID-19 Vaccination: A Case Report)

Table 1: Summary of NMOSD case reports (age, sex, serology, symptoms, MRI lesions, CSF findings, treatments, outcomes)

Case	Age/Sex	Serostatus (AQP4/MOG)	Presentation	MRI Findings	CSF Findings	Treatment(s)	Outcome	Ref
1	92/F	AQP4+ / MOG–	LETM (C4–T4, T9–12), area postrema syndrome	LETM C4–T12 (Fig. 1)[20]; new thalamic infarct	WBC 28 cells/µL, protein 0.64 g/L, OCB–[21]	IVIG + steroids, cyclophosphamide, satralizumab	Improved (EDSS 8→7), no relapse on satralizumab	11,16

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2	25/F	AQP4+ (4+) / MOG–	Area postrema syndrome, bilateral leg weakness	Brain: bilateral thalamus, occipital, medulla; Spine: LETM T7–L1[27]	Initial: WBC 250 (lymphocytes)[24], OCB not done; Later: not repeated	Steroids + PLEX, azathioprine, mycophenolate	Complete recovery of strength post-PLEX	28,113
3	49/F	AQP4+ (1:100) / MOG–	Paraplegia, sensory level (T4), urinary retention	LETM C6–T8 (Fig. 3)[30]	Normal (no pleocytosis)	Steroids + cyclophosphamide, IVIG, maintenance inebilizumab	Good recovery after inebilizumab	72,114
4	40/F	AQP4+ / MOG–	Right optic neuritis; later LETM (CML→C7)	LETM cervicomedullary to C7[32]	WBC 3 cells/μL; OCB–[32]	Steroids + PLEX, azathioprine	Near complete visual and motor recovery	81
5	35/F	AQP4– / MOG– (DN)	Recurrent LETM (T7–T10 x4), area postrema (nausea)	Recurrent LETM T7–T10	Pleocytosis (~20–30 cells/μL), OCB+, normal IgG index[33]	Steroids, MMF, rituximab (failed); then eculizumab	No relapses on eculizumab; EDSS 4→2[3]	95
6	69/M	AQP4+ / MOG–	Generalized weakness, sensory loss, incontinence	LETM C1–T12[35]	Not reported	Steroids + PLEX + IVIg	Partial motor recovery	99,115

Abbreviations: LETM = longitudinally extensive transverse myelitis; CSF = cerebrospinal fluid; OCB = oligoclonal bands; PLEX = plasma exchange; IVIG = IV immunoglobulin; EDSS = Expanded Disability Status Scale.

These cases underscore common NMOSD features (LETM on MRI, CSF pleocytosis) and

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heterogeneity in serology and age. AQP4+ patients (Cases 1–4,6) had astrocyte-targeted pathology, while Case 5 shows that even seronegative patients may benefit from complement-blocking therapy.

Discussion

This integrative study reveals two important notions relative to NMOSD: astrocyte injury drives AQP4+ pathology, and DN status provides manifestations that differ. **Interpretation.** This is most relevant where pathogenic AQP4-IgG dynamics occurs and significant astrocytic injury becomes evident in seropositive NMOSD*[1][10]* versus scant astrocytic biomarker prevalence in DNNMOSD*[2]. *Increased CSF GFAP within AQP4+ relapses corresponds to increased disability*[2,]* where DN-NMOSD CSF GFAP remains trivial, suggesting little compromise in astrocytes. Conversely, our series demonstrates similar findings — our seronegative Case 5 did not have astrocytic-directed autoantibodies; however, she still had relapses and responded to complement blockade, suggesting a final common pathway.

Imaging and Clinical Differences. Imaging lesion dissemination found in relatively similar percentages across populations, reflecting typical histopathologic features where AQP4 channels are abundant. All AQP4+ cases possessed LETM involving multiple segments*[20][27], *area postrema or brainstem engagement. Our seronegative Case 5 also demonstrated classic LETM T7–T10*[33]*. Thus, in NMOSD, where imaging criteria can be used independent of serostatus, this holds true. However, perhaps in DN-NMOSD cases, the brain MRI may be less prone to develop the stereotypical AQP4-pattern lesions (longitudinally extensive with periventricular projection) because the mechanisms of disease formation differ. Few relevant studies exist to provide tangible evidence to back up DN serological appearance in the brain.

Clinically, seronegative NMOSD has a lower relapse rate and better recovery from optic neuritis, but exceptions exist for cases*[3][13]*. This occurred in our series where the seronegative patient had ongoing relapses despite complemented blockade. The coexistence of autoimmunity (e.g. Sjögren's in Case 3) exists in AQP4+, but no reports exist in seronegative NMOSD. Instead, seronegative cases most often have no other autoimmune diagnosis.

Therapy Implications. Ultimately, all options available for NMOSD seek to focus upon antibody/complement axis reactions or B cells; thus, efficacy can also reflect the possibility in DN-NMOSD cases where mediating factors represent the same phenomena causing the cross-reactivity. We provide Case 5 a complete response on eculizumab, suggesting complement activation is a driving force either by other autoantibodies or innate mechanisms. Emerging clinical data (case reports/small case series) reveal that eculizumab and inebilizumab work for some seronegative patients; however, blinded studies have only admitted AQP4+ patients*[13]*

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thus far. Thus, in the meantime, clinicians act upon AQP4+ NMOSD protocols and evaluate patient response in DNNMOSD patients. For example, Case 3 represents the use of inebilizumab for an overwhelming disease that overlaps with autoimmunity.

Critique of Literature Currently/Classification. Literature within DN-NMOSD findings is sparse and often groups heterogeneous cases. Some seronegative "NMOSD" might possess unknown MOG antibodies (with advanced testing) or other etiologies (ex, glial fibrillary acidic protein astrocytopathy). The fact that DN-NMOSD does not have astrocytic injury*[2]* suggests they are truly NMOSD or an alternate astrocyte-sparing subtype? Current criteria per 2015 allow clinical diagnosis for NMOSD without serology if typical syndromes and imaging are observed*[5]*—but is this too inclusive? Potentially separates two distinct diseases. Future criteria may implicate biomarker findings (GFAP or IL-6) to assess subgrouping.

Unanswered Questions. Too many unknowns exist—what antigens drive relapses in DN-NMOSD, if any? Are T cells more important? Why do some respond to complement inhibition? The strikingly few patients with either antibody concurrently (AQP4 + MOG) further complicates data points. Autopsy data are scant across the NMOSD pathological setting, with limited speculation surrounding DN-NMOSD.

Therapy Limitations. Novel therapies have changed AQP4+ NMOSD management*[12][13]* for better and worse—increased cost and risk of infection from most agents (meningococcal sepsis with eculizumab) highlighted limitations of personal responsibility that could cloud assessment with certain patients who otherwise are compliant but unhealthy. Failures with MOGAD and DN-NMOSD raised significant gaps in clinical trialation history as one drug was investigated, but AQP4+ was only acknowledged. Other, more established options relative to azathioprine/MMF bear significant splenic observations without preference toward astrocytic versus myelin complications, which may suggest why findings vary across subcategories. Future therapies may aim at astrocyte protection/regeneration versus inflammatory avoidance.

Discussion Relative to Classification. Our findings support that AQP4+ NMOSD is inherently an astrocytopath, whereas DN-NMOSD may not belong to this category inherently. The notion that AQP4-independent NMOSD-like syndromes exist signals that "NMOSD" suggests something broader than a uniform immunopathology spectrum. Currently, the classification lumps all NMO-like syndromes into one where serology is negative; perhaps DN-NMOSD should be a temporary classification until definitive subtropics are discovered.

Limitations. This review occurred based on published case reports/open-access sources that could suggest publication bias (strikingly odd or severe cases more likely to be published). We were limited by the total DN-NMOSD cases published, as well as imaging figures impossible to

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obtain across the board. Thus, this case series is for illustrative purposes—not exhaustive.

Implications Based on Final Findings. Practical implications surround astrocytic centered observations—frequent AQP4-IgG monitoring predict relapses in certain seropositive but no correlating biomarkers exist for DNNMOSD; those reviewing our data would suggest CSF GFAP or serum neurofilament to assess potential injury between irritable insults versus decisive injuries; if unknowns occur—immunogenic focus should shift toward CSF monitoring relative to axonal/peripheral connection instead of pure serostatus—as precedent has set value that targetability works when recognizing immune effector pathways (complement/B cells/IL-6) involved instead of just nominal assumptions based on majority wins in immunologic focus per se retrospectively any patients clinically—thus limiting beneficial efficacy when it may be known under the surface instead aggressively assessed outside of the convalescing world despite efforts to try promote a delusional clarity at times.

Conclusion

NMOSD is a heterogeneous astrocyte-directed central nervous system disorder. Complement-mediated astrocyte injury differentiates AQP4+ NMOSD from complement-mediated demyelination and neurodegeneration*[1][10]*. In contrast, seronegative NMOSD lacks this predominant astrocytic injury, suggesting a different pathophysiology.

Through literature review and case report, we demonstrate that serostatus correlates with pathophysiological differences, but clinical management overlaps with a focus on aggressive immunotherapy. We call for attentiveness to the notion of “beyond the antibody”: astrocytic injury mediates much of AQP4+ NMOSD, but the presence of other mediating factors in seronegative NMOSD suggests different immune targets. Future studies should explore biomarkers (GFAP, cytokines) that allow for heterogeneous but more personalized approaches to NMOSD subtypes. Increased sensitivity and specificity of NMOSD diagnosis will result from more developed imaging and fluid markers for astrocytic injury, as well as larger-scale investigations. Improved NMOSD subtyping will increase clinical outcomes.

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