

## A Patient with NMO and Ulcerative Colitis: Is it only Autoimmunity?

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### Abstract

We report a case of a patient who developed neuromyelitis optica one year after discontinuation of her immunosuppressive agent used to treat her ulcerative colitis. We highlight the association between the two diseases that their similarities may not be limited to their autoimmune etiology, but also due to abnormal water channels, or aquaporins, and briefly discuss the possible role of aquaporins in ulcerative colitis pathogenesis.

**Keywords:** NMO; Ulcerative colitis; Aquaporin

### Case Report

A 35-year-old lady referred for recurrent bilateral severe optic neuritis. Her past medical history is significant for ulcerative colitis (UC) diagnosed in 2006 and treated successfully with azathioprine (AZA).

In August 2010, one year after AZA discontinuation, she had her first attack of severe right optic neuritis that caused blindness for which she received 5-day-course of intravenous methylprednisolone (IVMP) with complete recovery. Three months later, she had similar attack that was treated with another course of IVMP but with partial improvement. In May 2012 she had another episode of simultaneous bilateral severe optic neuritis not responding to 2 courses of IVMP. The MRI showed the enhancement of both optic nerves, chiasm, optic tracts, and lateral geniculate bodies (Figure 1a and 1b).

Upon presentation to our hospital 5 months after the last attack, she was blind and had no light perception. Her pupils were not reactive to light; she had pale optic discs, and otherwise normal neurological exam. A repeated MRI showed residual optic nerve atrophy with no brain or spinal cord lesions.

Patient's serum sent for neuromyelitisoptica (NMO) antibodies in Mayo clinic laboratories were positive with a titer of >1:160, and the diagnosis of NMO spectrum disorder (NMOSD) was confirmed. Other serological investigations showed negative rheumatoid factor, ANA, anti-DNA, anti-Ra, anti-La antibodies. A spinal tap showed normal levels of protein, glucose, and cells; oligoclonal bands were absent.

While the patient was scheduled to receive rituximab infusion, she had another relapse in December 2012 causing left sided weakness and hemianesthesia. The repeated MRI showed a "longitudinally extensive" lesion involving the right internal capsule and right cerebral peduncle (Figures 1b-1h). Her spine MRI was normal. She received 5-day-course IVMP with good recovery, followed by rituximab infusion of 1000 mg biweekly (Table 1).

Six months after treatment, her neurological exam came back to baseline and she continued to receive rituximab 1000 mg biweekly every 6 months. She also remains in remission from her ulcerative colitis since 2006.

### Discussion

Coexistence between NMO and both organ-specific and non-organ-specific systemic autoimmune diseases is not uncommon. In a cohort study of 153 patients with NMOSD, 4 (2.6%) patients diagnosed with ulcerative colitis, 26 (17.0%) with autoimmune thyroid disease, 5 (3.2%) with systemic lupus erythematosus or sjogren's syndrome, 2

with idiopathic thrombocytopenic purpura (1.3%), 2 with rheumatoid arthritis (1.3%), 2 with myasthenia gravis (1.3%), one with Raynaud phenomenon (0.7%), one with polymyositis (0.7%), and one with celiac disease (0.7%) [1]. A recent multinational study highlighted the association with acetylcholine receptor antibody positive myasthenia gravis (AChR-MG) [2]. Sixteen patients had both disorders, and four out of five patients whom stored sera where available had AQP4-IgG present 4 to 16 years before NMOSD onset [2]. Another case series suggested that those who underwent thymectomy maybe at higher risk for developing NMO [3,4]. Because of the association of two rare autoimmune diseases, authors suggested that patients diagnosed with AChR-MG might be at risk of developing NMO, and vice versa [2].

The association between NMO and UC is more interesting as they are not only two rare autoimmune disorders, but they share abnormalities in the water channels or aquaporin (AQP).

In 1991 Preston and Agre discovered a channel specific for water transportation formally called "CHIP28" for channel-like integral membrane protein of 28 kDa [5]. AQP are highly selective channels allowing water movement in response to osmotic gradient [6]. To date there are 13 subtypes of the AQP family in mammals [6,7].

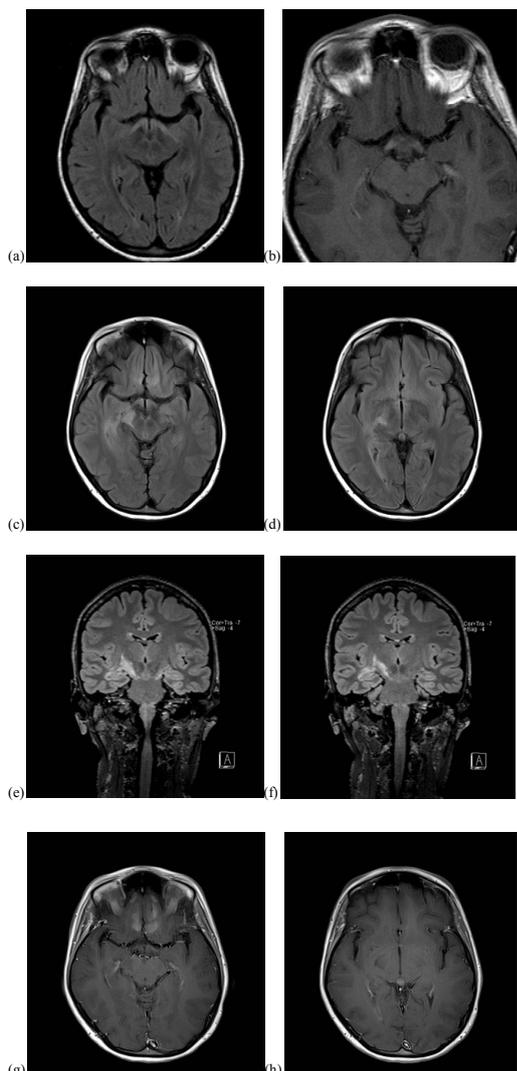
The role of AQP4 subtype is better understood in the CNS, as it is the most expressed water channel in the brain, spinal cord, and optic nerve. Its peculiar distribution on the astrocytic foot processes surrounding the endothelial cells and ependymal cells; i.e at the interface between brain paranchyma and perivascular space, and between brain and CSF has directed to the discovery of its critical role in maintaining the water homeostasis inside the CNS [8,9]. In 2004 the discovery of pathogenic IgG autoantibody against AQP4 in NMO has revolutionized the understanding of disease pathogenesis, aided in earlier identification, expanding its spectrum, and better targeted therapy [10]. The antibody demonstrated an excellent specificity (90%) and sensitivity (50%-90%) and was included in the 2006 revised diagnostic criteria for NMO [10,11].

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**Figure 1:** Axial FLAIR (a) images showing high signal intensity of the optic tracts bilaterally with diffuse enhancement post-contrast administration on T1 weighted images (T1WI) (b). Axial (c,d) and coronal (e,f) FLAIR showing continuous high SI of the right subcortical white matter, right posterior limb of the internal capsule, and right cerebral peduncle; the so called "longitudinally extensive" brain lesion with no enhancement post contrast administration on T1WI (g,h).

AQP function in the colon is of particular interest as it is one of the main organs responsible for maintaining body water homeostasis and its epithelium absorbs around 1.5-2 L/day [12]. While AQP4 has been detected in intestinal mucosa of mice and AQP4-knocked out mice produced feces with increased water content [13], no studies on human demonstrated the role of AQP4 in water transportation across its epithelium [14]. On the other hand human colonic mucosa is rich in AQP1, 3, 7, 8, and 11, and to lesser extent AQP4, 9, and 10 [12]. Human and animal studies showed that AQP8 and 7 may play an important role in fecal dehydration due its cellular distribution in the colon; AQP8 and 7 immunostaining was found in the apical surface of epithelial cells of proximal colon and rectum [14,15]. It also may play a role in UC pathogenesis as one study showed that immunostaining of human tissue biopsies from patients with moderate to severe UC revealed reduction in AQP8 and 7 [14]. The altered expression of AQP8 and 7 during colonic inflammation can explain the prominent symptom

Test	Result	Reference range
Anti-nuclear antibodies (ANA)	negative	≤ 1:40
CSF glucose	3.6 mmol/L	2.3-4.1 mmol/L
CSF protein	0.31 g/L	0.15-0.45 g/L
CSF WBCs count	0	0-5 cells/μL
CSF RBCs count	0	0-5 cells/μL
CSF oligoclonal bands	absent	
IgG index	0.55	0-0.77
Angiotensin converting enzyme (ACE)	32 units /L	8-52 units/L
Anticardiolipin antibodies (ACA) IgG	Negative GPL/ml	Negative <10 Equivocal 10-14 Positive >14
ACA IgM	Negative MPL/ml	Negative <7 Equivocal 7-10 Positive >10
ACA IgA	Negative APL/ml	Negative <7 Equivocal 7-10 Positive >10
Anti-SSA antibodies	Negative	Negative <20
Anti-SSB antibodies	Negative	Weak positive 20-30 Moderate positive 40-80 Strong positive >80
β2 Glycoprotein 1 IgG	Negative u/ml	Negative <10 Equivocal 10-14 Positive >14
β2 Glycoprotein 1 IgM	Negative u/ml	Negative <12 Equivocal 12-17 Positive >17
Lupus anti-coagulant LA1:LA2 Ratio	1.15	1.09-1.37
NMO IgG antibody	>1:160	<1:1.6

**Table 1:** Summarizes the most important laboratory tests.

of UC; diarrhea [14]. Another study showed opposite results with increased AQP8 expression in intestinal epithelium of non-inflamed mucosa and a subset of lamina propria mononuclear cells [16]. The authors suggested that early diarrhea is due to downregulation of AQP8 and later it is upregulated as a compensatory mechanism. There was also increased expression of AQP1, 3, and 11 in patients with UC [16].

Though the role of AQP in UC is still under discovery, the coexistence of UC in patients with pathogenic auto-antibodies against AQP4 or NMO raises the question about water channelopathy or "aquarinopathy" disorders. Perhaps individuals with one "aquarinopathy" disease like NMO are susceptible to another "aquarinopathy" like UC, and if such susceptibility exists early screening or watchful follow up is warranted before clinical appearance.

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All authors report no disclosure.

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