Neuromyelitis optica (NMO) is associated with severe neurodisability if not recognized and treated promptly. Several autoimmune disorders are associated with this condition and may vary in their presentation. It is essential that clinicians are aware of the uncommon presenting features of neuromyelitis optica and associated autoimmune conditions.

**Report of a Case**

A 53-year-old woman presented to her local accident and emergency department in October 2011 with nausea and vomiting. She was noted to have an asymptomatic elevated creatinine kinase level, which improved with conservative management. She had a history of iron-deficiency anemia due to long-standing celiac disease that was managed with a gluten-free diet. She then presented with recurrent transverse myelitis and a vesicobullous rash over her arms and feet that was pruritic and excoriating. Skin biopsy results confirmed a clinical diagnosis of dermatitis herpetiformis and antibody test findings against aquaporin-4 were positive, leading to a diagnosis of neuromyelitis optica spectrum disorder. She was treated with methylprednisolone sodium succinate, plasma exchange, and azathioprine and has remained in remission.
Results for anti-aquaporin-4 antibody (anti-AQP4 Ab) were positive and she was diagnosed as having NMO spectrum disorder (NMOSD).

Skin biopsy of the rash (Figure 3) showed neutrophilic infiltrates, intercellular edema, and bullae formation with ulceration in the epidermis. Immunofluorescence showed granular deposition of IgA and complement 3 at the dermoepidermal junction. These appearances were consistent with dermatitis herpetiformis (DH).

The patient was treated initially with methylprednisolone followed by 5 cycles of plasma exchange, with some improvement. She was treated with azathioprine along with prednisolone and has remained relapse free for the last 18 months. Her rash of DH has not worsened after instituting a strict gluten-free diet.

Written informed consent was obtained from the patient, and institutional review board approval was obtained as part of the UK Neuromyelitis Optica Study from the Walton Centre.

Discussion

Although relapsing longitudinally extensive transverse myelitis immediately raises the possibility of NMO, this case presented many additional diagnostic difficulties: the skin rash, elevated creatinine kinase level, nausea, and vomiting. Neuromyelitis optica is a relapsing autoimmune disorder characterized by longitudinally extensive transverse myelitis and optic neuritis and is associated with significant disability if untreated. A specific biomarker, an autoantibody against AQP4 (anti-AQP4 Ab), is extremely sensitive and specific for its diagnosis. The prevalence of autoimmune conditions, both organ and nonorgan specific, with NMO is approximately 30%.

Figure 1. Vesicobullous Excoriating Rash of Dermatitis Herpetiformis

Figure 2. Sagittal Cervical Spine T2-Weighted Magnetic Resonance Image Showing Longitudinally Extensive Transverse Myelitis

Figure 3. Histopathological Appearances of Dermatitis Herpetiformis

Skin biopsy from the left forearm showing to one side a relatively normal epidermis (A) and dermis (B). Adjacent to this, there is a neutrophilic infiltrate at the dermoepidermal junction (D) associated with intercellular edema within the epidermis. The neutrophilic infiltrate is dissecting the epidermis (C), forming an early microabscess/bulla. The upper part of the image shows an ulcer formed from the rupture of a bulla (E). These appearances are not pathognomonic of dermatitis herpetiformis and can be seen in cutaneous herpes infections, bullous pemphigoid, and impetiginized pemphigus vulgaris (hematoxylin-eosin, original magnification ×20).
The differential diagnosis for transverse myelitis associated with rash includes systemic lupus erythematosus, Behçet disease (rash is often a pathergy reaction), and antiphospholipid syndrome (livedo reticularis). It is increasingly recognized that systemic lupus erythematosus by itself rarely causes myelitis, and most patients with lupus myelitis have coexisting NMOSD. Many viral infections (herpes viruses 1 and 2, enterovirus, Epstein-Barr virus, cytomegalovirus, adenovirus, dengue, hepatitis A, varicella zoster, influenza, mumps, rubella, rubeola, human immunodeficiency virus, and human T-cell lymphotrophic virus 1) can cause myelopathy and rash. These were considered unlikely in our case. The biopsyped proven celiac disease in the gut and the characteristic rash narrowed the dermatological diagnosis to DH, which was confirmed on biopsy.

Dermatitis herpetiformis is considered an extraintestinal manifestation of celiac disease, an immune enteropathy triggered by wheat gliadin. Although there are several reports on the association of celiac disease with NMO (Table), very few mention the association of DH with NMO.6 The rash of DH is a chronic, pruritic, predominantly vesicobullous skin eruption.8 The pathophysiology involves IgA autoantibodies against transglutaminase 3, which are deposited and cause inflammation on the papillary dermis. The rash has been described as polymorphic: papular, vesicular, or bullous and extremely pruritic, leading to excoriations and crusted erosions. These often lead to hypo/hyperpigmentation and lichenification in chronic cases. The characteristic distribution is on the elbows, knees, gluteal region, neck, and shoulders. Dermatitis herpetiformis can present at any age and usually gets better in sunny weather owing to the beneficial effects of sunshine. Patients usually have a fluctuating course and spontaneous remission is rare. A skin biopsy shows findings of neutrophilic microabscesses at the papillary dermis tips, subepidermal bullae, and a granular IgA deposit on the papillary dermis. Several autoimmune disorders, such as thyroiditis, systemic lupus erythematosus, Sjögren syndrome, diabetes mellitus, primary biliary cirrhosis, pernicious anemia, vitiligo, alopecia areata, and pernicious anemia, are reported along with DH.9 Although the enteropathy (classic celiac disease) is quiescent in cases of DH, the small-intestinal changes of villous atrophy and crypt hyperplasia are usually present and may lead to malabsorption and iron deficiency. In addition, DH along with celiac disease share an increased risk for lymphoproliferative malignancies like non-Hodgkin lymphoma.10 The clinical differential diagnosis of the polymorphic rash seen in DH is wide and includes atopic dermatitis, herpetic infections, nummular eczema, dermatitis artefacta, scabies, or another immune blistering condition such as bullous pemphigoid. It is unlikely to be a hypersensitivity reaction to the medications used in the treatment of myelitis.

Another interesting feature in our reported case is the occurrence of hyperCKemia during the initial presentation. HyperCKemia has been reported in selected cases to precede the onset of NMO and also recur during the relapse.11 Aquaporin-4 has been expressed in the fast-twitch skeletal muscle fibers and its expression has also been noted to be altered in some dystrophic muscles. However, muscle diseases have not been reported in NMO and the exact correlation of hyperCKemia with NMO is not fully understood. One postulation is that muscle destruction due to anti-AQP4 Ab augments cellular and humoral autoimmunity to AQP4 and triggers disruption of the blood-brain barrier and influx of the antibodies causing inflammation of the central nervous system.12 Nausea, vomiting, and hiccup are associated with NMO. These represent brainstem involvement (area postrema) and may precede an episode.13 The presence of these in the absence of a gastrointestinal cause should alert the physician to a brainstem pathology including NMO.

This report aimed to highlight 3 aspects of NMOSD. First, the coexistence of DH with NMOSD. Because DH occurs mostly without symptoms of enteropathy, it is important to suspect a vesicobullous pruritic rash as DH and confirm the diagnosis with a dermatology consult, skin biopsy, and, if appropriate, small-bowel biopsy. Second, nausea and vomiting can be a presentation of NMOSD. Third, hyperCKemia can occur in NMO and is possibly related to skeletal muscle involvement. The presence of anti-AQP4 Ab supports NMOSD, predicts future relapses, and alerts the clinician to consider early immunomodulatory treatment and prompt aggressive treatment of relapses.

### Table. Summary of Cases of Neuromyelitis Optica Spectrum Disorder Associated With Celiac Disease

<table>
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<tr>
<th>Source</th>
<th>Patient No.</th>
<th>Sex</th>
<th>Age at CD Diagnosis, y</th>
<th>AGA/TTG</th>
<th>Biopsy*</th>
<th>Age at NMO Diagnosis, y</th>
<th>Anti-AQP4 Ab</th>
<th>No. of ON Episodes</th>
<th>No. of LETM Episodes</th>
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<tr>
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</table>

Abbreviations: AGA, antigliadin antibody; anti-AQP4 Ab, anti–aquaporin-4 antibody; CD, celiac disease; F, female; LETM, longitudinally extensive transverse myelitis; NK, not known; NMO, neuromyelitis optica; ON, optic neuritis; TTG, tissue transglutaminase antibody.

* Small-bowel biopsy confirming CD.
ARTICLE INFORMATION
Accepted for Publication: December 16, 2013.
Published Online: March 17, 2014.
Author Contributions: Drs Iyer and Jacob had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Iyer, Jacob.
Acquisition of data: Iyer, Rathnasabapathi, Elsone, Mutch.
Analysis and interpretation of data: Iyer, Rathnasabapathi, Elsone, Terlizzo, Footitt, Jacob.
Drafting of the manuscript: Iyer, Rathnasabapathi, Elsone, Jacob.
Critical revision of the manuscript for important intellectual content: Elsone, Mutch, Terlizzo, Footitt, Jacob.
Administrative, technical, and material support: Iyer, Rathnasabapathi, Elsone, Mutch, Terlizzo, Footitt.
Study supervision: Jacob.
Conflict of Interest Disclosures: Dr Elsone has received travel grants to attend scientific meetings from Teva and Novartis. Dr Jacob has received honoraria for speaking on neuromyelitis optica and for clinical trial advisory boards from Biogen, Chugai, and Terumo BCT. No other disclosures were reported.

REFERENCES