Neuromyelitis Optica and Skin

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Keywords

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Abstract

Neuromyelitis optica spectrum disorder is characterized by attacks of optic neuritis and/or longitudinally extensive transverse myelitis and the presence of anti-aquaporin-4 autoantibodies. Most relapses of neuromyelitis optica worsen over days and then slowly improve in the weeks or months after the maximum clinical deficit has been reached. However, recovery is usually incomplete. The diagnosis of the disease and attacks must be made as early as possible and require emergency treatment. Dermatologists can play a role in achieving this end. Neuropathic pruritus is common and can be used to diagnose neuromyelitis optica. Hence, the association of pruritus with optic neuropathy and some symptoms of transverse myelitis strongly suggest this diagnosis. Many autoimmune diseases can sometimes be associated with neuromyelitis optica. Patients with newly diagnosed skin infections or sexually transmitted diseases need to be informed that these infections could trigger a relapse of neuromyelitis optica.

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Introduction

Neuromyelitis optica (also known as Devic's disease) is an idiopathic, severe, demyelinating disease of the central nervous system that preferentially affects the optic nerve

and spinal cord. Neuromyelitis optica has a worldwide distribution, poor prognosis, and has long been thought of as a variant of multiple sclerosis; however, clinical, laboratory, immunological, and pathological characteristics that distinguish neuromyelitis optica from multiple sclerosis are now recognized [1]. In particular, the detection of neuromyelitis optica immunoglobulin G (NMO-IgG), an autoantibody that binds to aquaporin 4 (AQP4), in the serum of patients with neuromyelitis optica distinguishes neuromyelitis optica from other demyelinating disorders [2]. Neuromyelitis optica is up to 9 times more prevalent in women than in men, and the median age of onset is 40 years [1].

Neuromyelitis optica is a neurological disease that is poorly known by dermatologists because there are very few papers on this topic in the dermatological literature [3, 4]. However, neuromyelitis optica is a cause of neuropathic pruritus [5] and can be associated with other autoimmune diseases [6].

Diagnosis of Neuromyelitis Optica

Eugène Devic and Fernand Gault in Lyon described a new disease characterized by the association of optic neuritis and acute transverse myelitis in 1894 [7]. It remained unclear whether neuromyelitis optica was a separate disease or merely a more severe form of "opticospinal" multiple sclerosis until 2004, when the two diseases could be reliably distinguished through the detection of anti-AQP4 antibodies [8].

Neuromyelitis optica is a rare disease: the incidence and prevalence of neuromyelitis optica spectrum disorder (NMOSD) range from 0.05 to 0.40 and 0.52 to 4.4 per 100,000 people, respectively [8]. Although diagnosis is frequently delayed, clinical manifestations are very evocative [1]. Attacks of optic neuritis and myelitis usually occur sequentially rather than simultaneously at intervals ranging from years to decades. Ocular pain with loss of vision, myelitis with severe symmetric paraplegia, sensory loss below a lesion, and bladder dysfunction are typical features of neuromyelitis optica. Cervical myelitis can extend into the brainstem, resulting in nausea, hiccoughs, or acute neurogenic respiratory failure. Other typical symptoms of spinal cord demyelination include paroxysmal tonic spasms (recurrent, stereotypic painful spasms of the limbs and trunk that last 20–45 s) and Lhermitte's symptom (spinal or limb dysaesthesias caused by neck flexion). Attacks are frequently severe and often reach the nadir in less than a week. Hypothalamic periventricular regions may be affected, inducing hypothalamic hypocretin neuronal function. Several cases of narcolepsy have been reported. Brain involvement can be seen in 60% of patients, although the majority of observed changes are non-specific. Cerebral involvement may be asymptomatic but can cause encephalopathy, seizures, and hemiparesis.

At the onset of neuromyelitis optica, the brain magnetic resonance imaging (MRI) usually does not show any abnormality, except for optic nerve enhancement by intravenously administered gadolinium during an acute attack of optic neuritis or the presence of non-specific, white matter lesions. Brainstem lesions can occur. MRI findings for the spinal cord have great diagnostic utility: during myelitis attacks, lesions imaged with T2-weighted MRI are longitudinally extensive and characteristically span 3 or more contiguous vertebral segments [1].

In cerebrospinal fluid, pleocytosis ($>50 \times 10^6$ leucocytes/L) with a high proportion of neutrophils is characteristic of neuromyelitis-optica-specific myelitis. Supernumerary oligoclonal bands of IgG are sometimes detected, but less frequently than in patients with multiple sclerosis [1].

The term “neuromyelitis optica spectrum disorders” (NMOSD) was introduced in 2007 to include recurrent or bilateral optic neuritis and longitudinally extensive transverse myelitis (LETM) in addition to classical neuromyelitis optica [9]. In 2015, NMOSD was proposed as a unifying term to cover the entire clinical spectrum of this disease, including limited forms of neuromyelitis optica, such as recurrent optic neuritis, or the first attack of

LETM for patients who are at high risk of recurrence and different brain manifestations, such as area postrema syndrome, brainstem syndrome, and diencephalic syndrome. International consensus diagnostic criteria have been defined for NMOSD [10] (Table 1).

Recent studies have shown that anti-AQP4 antibodies may be absent in 20–30% of NMOSD cases, whereas anti-myelin oligodendrocyte glycoprotein antibodies have been detected in a good proportion of AQP4-seronegative cases of NMOSD [9]. Myelin oligodendrocyte glycoprotein-associated disease has overlapping clinical and radiological features with AQP4-positive NMOSD but is now seen as a distinct disease entity [9]. In patients with this new entity [11], no dermatological associations have been reported thus far but may be identified by further study.

Neuromyelitis Optica as a Cause of Neuropathic Pruritus

Neuropathic itch (or pruritus) refers to pruritus caused by neuronal or glial damage [5]. Neuropathic itch is usually associated with other symptoms, such as pain, allodynia, paraesthesias, hyperaesthesia, hypoaesthesia, and twinges or electric shock sensations. Neuropathic itch can also be aggravated with activity and relieved with cold, and a questionnaire has been proposed to aid diagnosis: the Neuropathic Pruritus – 5 Questions [12]. Neuropathic itch is more commonly associated with disorders of the peripheral nervous system than the central nervous system (Table 2) [5]. Among these central nervous system disorders, neuromyelitis optica has recently been reported to be a cause of neuropathic pruritus [9].

The first study on patients with NMOSD myelitis was conducted in 2012, in which 12 out of 44 patients (27.3%) reported pruritus within a week of other symptoms of transverse myelitis with central cord involvement [13]. Pruritus was the first symptom of relapse in 3 patients and the very first symptom of the index episode of neuromyelitis optica in 1 case. This symptom was considered a consequence of the inflammation of itch-specific fibres in the spinothalamic tract.

A multicentre study was performed in which various brainstem signs were searched for in 258 patients [14]. Eighty-one patients presented with the following symptoms: vomiting (33.1%), hiccups (22.3%), oculomotor dysfunction (19.8%), pruritus (12.4%), hearing loss (2.5%), facial palsy (2.5%), vertigo or vestibular ataxia (1.7%), trigeminal neuralgia (2.5%), and other cranial nerve signs (3.3%). These symptoms were inaugural in 44

Table 1. International diagnostic criteria for neuromyelitis optica spectrum disorders [10]

Diagnosis with AQP4 antibodies

- 1 At least 1 core clinical characteristic
- 2 Positive AQP4 antibodies with best available method
- 3 Exclusion of alternative diagnosis (e.g., sarcoidosis, neoplastic/paraneoplastic, vascular, chronic infection)

Diagnosis without AQP4 antibodies/unknown status

- 1 At least 2 core clinical characteristics resulting from 1 or more clinical attacks and fulfilling the following:
 - a At least 1 of optic neuritis, LETM, APS
 - b Dissemination in space (2 or more different core clinical characteristics)
 - c Fulfilment of additional MRI requirements as applicable
- 2 Negative for AQP4 antibodies with best available method, or testing unavailable
- 3 Exclusion of alternative diagnoses

Core clinical characteristics

- 1 Optic neuritis
- 2 Acute myelitis
- 3 APS
- 4 Brainstem syndrome
- 5 Symptomatic narcolepsy or acute diencephalic syndrome with NMOSD-typical diencephalic MRI lesions
- 6 Symptomatic cerebral syndrome with NMOSD-typical brain lesions

Additional MRI requirements for NMOSD without AQP4 antibodies/unknown status

- 1 Acute optic neuritis: normal or only non-specific white matter lesions on MRI of the brain, or optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or optic chiasm involvement
- 2 Acute myelitis: MRI spinal cord demonstrating attack associated lesion spanning ≥3 contiguous vertebral segments (LETM) or ≥3 contiguous segments of focal cord atrophy with previous history of acute myelitis
- 3 APS: dorsal medulla/area postrema lesion on MRI of the brain
- 4 Acute brainstem syndrome: peripendymal brainstem lesions

APS, area postrema syndrome; AQP4, aquaporin-4; LETM, longitudinally extensive transverse myelitis; NMOSD, neuromyelitis optica spectrum disorder; MRI, magnetic resonance imaging.

patients (54.3%). The prevalence of symptoms was higher in AQP4-antibody-seropositive patients (32.7%) than in seronegative patients (26%) (not significant).

In a Chinese study, a review of the case records of 64 NMOSD patients revealed that 18 (28.1%) had pruritus [15]. Spinal MRI showed lesions in all the patients in the study. A total of 13 patients presented with brain lesions, and 4 had lesions in the periaqueductal grey matter on the cerebral MRI. Surprisingly, the anatomical distribution of pruritus did not always correspond to the dermatomal distributions of the involved spinal cord segments because the itching locations were smaller than, or even different from, the dermatomal distributions of the involved spinal cord segments in some patients. Pruritus was completely or partially relieved after treatment.

In another Chinese study, 52 of 230 NMSOD patients (22.61%) were found to experience painful tonic spasms. These 52 patients were characterized by a higher age at onset, higher annual relapse rate, higher number of myelitis relapses, and a tendency to experience pruritus ($p = 0.025$) [16].

Table 2. Neurological disorders from the central nervous system which can induce neuropathic pruritus

Tumours
Abscess
Aneurysms
Cerebrovascular accidents
Creutzfeldt-Jakob disease
Multiple sclerosis
Neuromyelitis optica spectrum disorder
Syringomyelia
Transverse myelitis
Post-traumatic Brown-Séquard syndrome

A new study was performed on 61 patients with NMOSD [17]. Among these patients, 59 had LETM, out of which 38 (64.4%) reported pruritus during the course of their illness, and 16 reported pruritus as an initial symptom followed by limb weakness. In 35 of the aforementioned 38 patients (92.1%), pruritus was located within the dermatomes innervated by the spinal nerves

from the involved spinal cord. The authors concluded that pruritus may indicate a new episode of myelitis in patients with NMOSD.

The same authors performed a retrospective study in which 21.0% of NMOSD patients (22/105) reported pruritus during disease compared to only 2.1% (2/96) among patients with multiple sclerosis ($p < 0.01$). A total of 20.5% (18/88) of AQP4-IgG-positive and 23.5% (4/17) of AQP4-IgG-negative NMOSD patients reported pruritus during the disease course ($p = 0.775$) [18]. A total of 12.4% (13/105) of NMOSD patients and 1.0% (1/96) of patients with multiple sclerosis reported pruritus at the first attack episode of disease ($p < 0.01$). A total of 20.0% (21/105) of NMOSD patients and 1.0% (1/96) of patients with multiple sclerosis reported pruritus at the first and second attack episodes of disease ($p < 0.01$). Hence, neuropathic pruritus is more indicative of NMOSD than multiple sclerosis. Moreover, the frequencies of pruritus that were reported before the discovery of anti-AQP4 antibodies as a specific marker of neuromyelitis optica could be erroneous, and pruritus can be considered an indicator of NMOSD in the presence or absence of anti-AQP4 antibodies [18].

In all studies, most NMOSD patients had other sensory symptoms in the pruritus region, suggesting that the dorsal horn or trigeminal spinal nucleus might be involved in most patients with pruritus and that had lesions located centrally within the spinal cord [18]. Consequently, grey-matter involvement of the spinal cord should be the main cause of pruritus, and pruritus is probably secondary to spinal cord neuronopathy but not demyelination. The increased frequency of a centralized location of lesions in the spinal cord affecting dorsal horn neurons in NMOSD compared to multiple sclerosis contributes to the significantly higher reported rate of pruritus in NMOSD than in multiple sclerosis [18]. In addition, in some NMOSD patients, the pruritus location did not correspond to dermatomal distributions of the involved spinal cord segments, indicating that pruritus-processing entities, such as pruritus-associated neurons in the spinothalamic tract, might be involved [18]. Note that the majority of NMOSD patients with pruritus had neuropathic pain at the pruritus region, suggesting that the lesion location affects symptoms of neuropathic pruritus and neuropathic pain together [18].

Pathophysiology of Neuromyelitis Optica

The role of astrocytes in chronic itch has been known for some years [19]. The presence of intractable itch in neuromyelitis optica shows that astrocytes can be in-

involved in acute itch. In neuromyelitis optica, astrocytes probably induce neuronal damage, which is directly responsible for pruritus.

Hence, the target of autoantibodies is AQP4, a water channel identified in astrocytes [2]. AQP4 is a water-channel protein expressed in the end feet of astrocytes of the central nervous system (especially those of the spinal cord, optic nerves, and perivascular areas) and to a lesser extent in ependymal cells. AQP4 facilitates water movements between the blood, brain, and cerebrospinal fluid compartments, the migration of astrocytes and scar formation by glial cells, neural signal transduction, and neuroinflammation [9]. Anatomically, AQP4 is located in regions in contact with cerebrospinal fluid [8].

The binding of the AQP4 antibody (IgG1) to the AQP4 protein on the surface of astrocytes results in various functional consequences, including target internalization, impairment of AQP4 function, complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity [20]. Complement activation leads to the recruitment of activated macrophages, releasing cytokines and oxygen free radicals, which leads to a secondary event, the destruction of neurons and oligodendrocytes [21].

Finally, astrocytic destruction, rather than demyelination, is the pathological hallmark of AQP4-positive NMOSD [9]. In contrast to multiple sclerosis, the demyelination that is seen in AQP4-positive NMOSD is a secondary event and occurs as a consequence of primary damage to astrocytes [8]. Demyelination in neuromyelitis optica extends across multiple sections of the spinal cord, inducing necrosis and cavitation of both grey and white matter in the spinal cord (with subsequent LETM) and optic nerve lesions [1].

Association of Neuromyelitis Optica with Other Autoimmune Diseases

The role of aquaporins in skin biology and physiology is very well known. Aquaporins are crucial for skin hydration, implicated in wound healing and epidermal barrier repair, and involved in sweat secretion and other physiological mechanisms [22]. Consequently, aquaporins may be involved in the pathophysiology of some skin diseases [23]. Knockout models have revealed that aquaporins facilitate cell migration, as seen in aquaporin-dependent tumour angiogenesis and tumour metastasis, transport both glycerol and water, regulate glycerol content in the epidermis, fat, and other tissues, and lead to a multiplicity of interesting consequences of gene disruption, in-

cluding dry skin, resistance to skin carcinogenesis, impaired cell proliferation, and altered fat metabolism [24]. In any case, AQP4 has never been identified in the skin, and no skin symptoms have been directly related to the presence of specific antibodies. Consequently, pruritus is not a direct effect of antibodies on the skin itself.

Nonetheless, dermatological symptoms may be related to the association of neuromyelitis optica with autoimmune diseases [6]. The association of neuromyelitis optica with other autoimmune diseases could be related to a genetic predisposition, because AQP4 IgG positivity has been found to be associated with HLA-DRB1*03 (DR3) in French and Brazilian populations and with HLA-DPB1*0501 in Japanese and Chinese populations [9].

Hence, diseases with immune-based pathogenesis are the most frequently reported comorbidities associated with NMOSD, most of which are antibody-mediated diseases. According to a literature review [6], Sjögren's syndrome and systemic lupus erythematosus are the most frequently reported diseases associated with NMOSD among systemic autoimmune diseases. Furthermore, myasthenia gravis in neurological and autoimmune thyroid diseases in non-neurological organ-specific autoimmune diseases are the most reported comorbidities associated with NMOSD in the literature [6]. Sarcoidosis, systemic sclerosis, or antiphospholipid syndrome have also been reported.

Raynaud's phenomenon has been found to be the most common specific skin disorder associated with NMOSD. Other cutaneous disorders, such as dermatomyositis, dermatitis herpetiformis, pemphigus foliaceus, psoriasis, bullous pemphigoid, pyoderma gangrenosum, vitiligo, atopic dermatitis, alopecia aerata, and limited scleroderma, have been reported to be associated with NMOSD [6].

Other Associations of Neuromyelitis Optica and Skin Disorders

An unusual case was reported of a patient who developed NMOSD after a yellow fever vaccination that was associated with painful erythema triggered by touch in the respective skin area due to a cervical spinal cord lesion affecting the dorsolateral parts of C_{6/7} [25].

Infections are known to trigger disease onset and relapse in NMOSD. Viral infections are known to precede NMOSD in 15–35% of cases. The most common viral infection is VZV, often in combination with HIV. Other viral infections include CMV, EBV, dengue and hepatitis A virus. Among bacterial infections, *Mycobacterium tu-*

berculosis, *Mycoplasma pneumoniae*, and *Treponema pallidum* have been reported in the literature [9, 26]. A systematic review showed an association between SARS-CoV-2 infection and the development of different demyelinating diseases, including NMOSD [27].

Notably, interferon- α was reported as being able to induce or reveal NMOSD in the case of 1 patient being treated for melanoma [28].

Prognosis and Management of Neuromyelitis Optica

Neuromyelitis optica is usually characterized by relapsing episodes, a monophasic course being exceptional. Most relapses of neuromyelitis optica worsen over several days and then slowly improve in the weeks or months after the maximum clinical deficit has been reached. However, recovery is usually incomplete, and most patients follow a course of early incremental disability due to frequent and severe relapses [1]. Within 5 years of disease onset, more than 50% of patients with relapsing neuromyelitis optica are blind in 1 or both eyes or require ambulatory help [1]. Predictors of a poor prognosis include the number of relapses in the first 2 years of disease activity, the severity of the first attack, and, possibly, systemic lupus erythematosus or a related non-organ-specific autoimmune disorder or autoantibodies. The 5-year survival rate for neuromyelitis optica had been estimated at 68%, with all deaths being due to neurogenic respiratory failure [1]. Fortunately, more recent studies have estimated a 5-year survival rate of 98% [9] due to the progress that has been made in diagnosis and treatment.

Consequently, management consists of an early diagnosis, urgent treatment of acute attacks and a long-term maintenance therapy to reduce the risk of relapse [9]. Dynamic clinical research is a moral obligation.

Acute NMOSD attacks are treated with high-dose corticosteroids, with plasmapheresis or intravenous immunoglobulins as second options [8, 9, 20]. Maintenance therapy includes the administration of azathioprine or mycophenolate mofetil and, less commonly, methotrexate or cyclophosphamide. Encouraging results have been obtained from clinical trials on the use of rituximab (anti-CD20), eculizumab (anti-C5), satralizumab (anti-IL6-R), tocilizumab (anti-IL6-R), or other biotherapies [8, 9, 20]. Preclinical data suggest that the effects of pathological autoantibodies can be blocked by aquaporin, an anti-AQP4 antibody in which the antibody Fc portion has been mutated to eliminate effector functions involved in complement- and cell-mediated cytotoxicity [29].

Conclusion

Neuromyelitis optica is a rare but severe neurological disorder whose diagnosis must be made as soon as possible to enable rapid and appropriate treatment. The dermatologist can play a role in the diagnosis of neuromyelitis optica. Indeed, severe pruritus is relatively frequent in neuromyelitis optica compared to other inflammatory demyelinating diseases, such as multiple sclerosis. This frequency is probably related to the pathophysiological mechanism that leads to lesions of medullary neurons of the spinothalamic tract secondary to astrocytic destruction mediated by the presence of anti-aquaporin antibodies.

Thus, the presence of pruritus in a patient with optic neuropathy or transverse myelitis strongly suggests a neuromyelitis optica diagnosis.

Key Message

Neuromyelitis optica is poorly known by dermatologists but is a cause of neuropathic pruritus and it can be associated with skin diseases.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.M. performed the bibliographical research and wrote the paper. S.G. and F.Z. revised the paper.

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