**PERSPECTIVES**

**OPINION**

**Pain in neuromyelitis optica—prevalence, pathogenesis and therapy**

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**Abstract** | Terrible, agonizing, wretched, sickening and unbearable—these are words frequently used by patients with neuromyelitis optica (NMO) to describe a very common symptom of their disease: pain. More than 80% of patients with NMO experience pain from this condition, which severely affects their quality of life. At present, there is no known therapy that produces satisfactory relief from NMO-associated pain. In fact, contemporary pain therapy is largely ineffective in these patients, suggesting that the mechanisms underlying pain in NMO differ substantially from those of other treatable causes of pain. Until now, the near-complete neglect of research into pain mechanisms in NMO has precluded rational pain therapy. In this Perspectives article, expertise from the fields of neuroimmunology, neurology and pain research is combined to explore, for the first time, the mechanisms underlying pain in patients with NMO, and to identify molecular and cellular targets for therapy.

**Introduction**

Neuromyelitis optica (NMO; also known as Devic disease) is a severe autoimmune disease of the CNS that occurs in individuals of all ethnicities. In the vast majority of patients, serum antibodies are found against the water channel aquaporin-4 (AQP4). In the CNS, AQP4 is primarily localized to astrocytic processes at the subpial and perivascular glia limitans (forming the interfaces between the CNS and the cerebrospinal fluid and blood, respectively), and to ependymal cells and subependymal astrocytic processes that form the CNS–cerebrospinal fluid interface. Antibodies against AQP4 represent a highly specific biomarker for NMO, and have an important role in the initiation and propagation of the astrocyte-destructive lesions that are characteristic of this disease.

The clinical presentation of NMO includes severe episodes of optic neuritis causing loss of vision, transverse myelitis causing paraplegia or paralysis, and—in some patients—periods of brainstem encephalitis causing intractable vomiting or hiccups. Many patients with NMO experience pain that severely affects their quality of life, and which is currently often refractory to treatment. As discussed in this article, better knowledge about the underlying mechanisms of pain in individual patients with NMO could provide the basis for personalized analgesic therapy.

**Prevalence of pain in NMO**

Pain is highly prevalent in patients with NMO, with two types of pain being most characteristic: evoked pain most often caused by painful tonic muscle spasms, and ongoing neuropathic pain. In a Korean cohort of 40 patients with NMO, painful tonic spasms were observed in 25% of cases. Painful tonic spasms were experienced in either the legs or the arms in some patients, in all extremities in others, and in only one limb in a third group. Muscle spasms most frequently occurred within a mean of 48 days of the first myelitis episode of NMO, and were not accompanied by new neurological deficits or new MRI lesions. This form of NMO-related pain is currently treated with sodium channel-blocking antiepileptic agents such as carbamazepine, gabapentin, clonazepam and phenytoin sodium. In addition, the muscle spasms can be attenuated by muscle relaxants, antiparkinsonian drugs and physiotherapy.

Patients with NMO also develop severe, intractable and ongoing neuropathic pain. The painful areas are located around the chest and waist, along the entire length of the legs, or in the back. Quantitative sensory testing of patients with NMO reveals mechanical and thermal sensory loss correlated with ongoing pain; thermal and heat hyperalgesia; and dysesthesias such as dynamic mechanical allodynia and paradoxical heat sensations. The severity of NMO-associated pain does not correlate with the duration of the disease, age, AQP4 antibody status or the number of relapses. In fact, severe agonizing pain can occur in the early stages of the disease and can even be the first clinical symptom of NMO. At this stage in diagnosis, the painful area usually corresponds to the location of spinal cord lesions found on MRI. Moreover, spontaneous pain in one affected area (for example, the thorax) can occur at the same time as impaired sensation of touch, evoked pain and vibration in other areas (for example, the limbs), and can coexist spatiotemporally with neuropathic pruritus (Table 1).

NMO-associated neuropathic pain is often refractory to treatment, despite the availability of a large variety of pain medications, each targeting different pain mechanisms, and multiple drug combinations.

**Principles of nociception**

Nociception is characterized by excitation of nociceptive nerve endings, which are present in all peripheral organs and skeletal muscles. Nociceptive nerve fibres are either thin, unmyelinated Aδ fibres or thinly myelinated Aβ fibres that project via the dorsal root entry zone to terminate in superficial laminae I and II of the spinal dorsal horn. In these laminae, the fibres make excitatory glutamatergic synaptic contacts with spinal dorsal horn neurons, some of which project to the brain after crossing over to the contralateral side at the spinal level near the central canal.

Importantly, nociceptive signalling is subject to considerable modulation even at the level of the spinal cord, and strongly depends on the activation states of astroglia.
The specific activation pattern of brain nuclei determines the type of pain experienced by a given patient. The brain, however, is not a passive recipient of nociceptive information: via long descending pathways, it actively modulates its own nociceptive input arriving from the spinal cord. In fact, the spinal transmission of nociceptive information is under powerful inhibitory control originating from the midbrain periaqueductal grey (Figure 1) or medullary nuclei. The descending inhibitory fibres from this region release noradrenaline or serotonin in the spinal dorsal horn to suppress nociception either directly or indirectly via inhibitory interneurons. Clinically relevant forms of central pain amplification and pain generation can, thus, emerge from two fundamental neuronal processes: enhanced excitation and reduced inhibition.

**Pathological substrate of pain**

The pathogenesis of NMO has been extensively reviewed elsewhere, so here we focus only on those aspects that are of potential relevance to the development of pain. Spinal cord lesions in patients with NMO predominantly affect the cervical and thoracic spinal cord and extend over three or more vertebrae. Owing to the more abundant expression of AQP4 in grey than in white matter, these lesions tend to be located mainly around the central canal and the adjacent grey matter in the dorsal and ventral horns of the spinal column (Figure 1). The ascending and descending tracts in the spinal white matter are only affected in severe and extensive lesions. In addition, lesions regularly affect the dorsal horn and the dorsal root entry zone. About 10–15% of all patients with NMO have linear medullary lesions, which are mainly located in the floor of the fourth ventricle, and expand into the mesencephalon along the periaqueductal grey (Figure 1). In addition, lesions are frequently seen in the basal hypothalamus or adjacent to the third ventricle. We can conclude, therefore, that NMO lesions involve many CNS structures that are either adjacent to or contain nociceptive or antinociceptive pathways (Figure 1).

Typically, astrocyte injury in NMO is initiated by the binding of AQP4-specific autoantibodies to the surface of these cells, and damage is mediated by complement activation or the interaction of activated effector cells with antibody-opsonized astrocytes. This process is associated with—and potentially triggered by—an...
inflammatory response consisting of T lymphocytes, activated macrophages and microglia, as well as granulocytes.\textsuperscript{24}

Initial astrocyte injury in developing NMO lesions might have additional consequences for tissue homeostasis. Loss of AQP4, which is seen broadly in areas surrounding NMO lesions, might disturb water homeostasis even when astrocytes are preserved,\textsuperscript{44} although this finding has not been confirmed by other studies.\textsuperscript{25} This disruption of water homeostasis might be augmented by loss of AQP1 expression from astrocytes in the lesions.\textsuperscript{25} Furthermore, AQP4 is coexpressed with other molecules in lipid raft domains, which are lost in parallel during initial tissue injury in NMO lesions. Important candidates include excitatory amino acid transporter 2 (EAAT2), which has an essential role in glutamate buffering in astrocytes.\textsuperscript{76,77} Thus, initial NMO tissue injury might lead to excessive accumulation of glutamate in the extracellular space, inducing aberrant neuronal excitation and excitotoxic tissue injury. Other potentially important molecules that are lost in the early stages of NMO pathology include connexins, which form gap junctions between different astrocytes or between astrocytes and oligodendrocytes.\textsuperscript{38,39} Disruption of functional connectivity between glial cells might propagate excitotoxic tissue injury or even initiate oligodendrocyte degeneration.\textsuperscript{25,40}

Astrocyte destruction is followed by oligodendrocyte injury and subsequent axon demyelination.\textsuperscript{37,41} In parallel with demyelination, acute axonal injury and axonal loss occur.\textsuperscript{24} Thus, the final NMO lesion reflects a highly destructive process, which leads to the formation of cystic cavities interspersed with bridges of preserved axons and reactive astrocytes forming glial scars. Signs of axon remyelination or repair are sparse.\textsuperscript{25}

**Lesion development and pain**

In the absence of inflammatory lesions in the CNS, patients with NMO and serum autoantibodies against AQP4 have no functional deficits and do not experience particular pain states.\textsuperscript{45} However, this situation changes drastically with ongoing lesion formation.

**Early active NMO lesions**

In early stages of lesion formation and at the borders of active lesions, astrocytes are activated and no longer express AQP4.\textsuperscript{25} Activation of microglia in and recruitment of macrophages and neutrophilic granulocytes to these lesions leads to the production and release of a large number of cytokines (including IL-1β, IL-6, IL-17 and tumour necrosis factor [TNF]), chemokines,\textsuperscript{20,43} and growth factors such as brain-derived neurotrophic factor (BDNF), all of which might have important roles in the pathogenesis of NMO and might exert strong pronociceptive effects (Table 2). Consistent with this idea, in animal models of experimental autoimmune encephalomyelitis, CNS neuroinflammation is a key mediator of thermal hyperalgesia and allodynia.\textsuperscript{14,44}

Glutamate is the principal excitatory neurotransmitter in the first synaptic relay of nociceptive pathways in laminae I and II of the spinal dorsal horn. Both IL-1β and TNF might enhance glutamatergic signalling and, thus, the strength of synaptic transmission between nociceptive C fibres and neurons in spinal laminae I and II.\textsuperscript{45,46} Opening of glutamatergic Ca\textsuperscript{2+}-permeable N-methyl-d-aspartate (NMDA) receptors triggers long-term potentiation (LTP) at C-fibre synapses, which is considered a key cellular mechanism for long-lasting pain amplification (hyperalgesia).\textsuperscript{47,48}

IL-17 might enhance NMDA receptor-mediated pronociceptive effects in the spinal dorsal horn, as suggested by the phosphorylation of the NMDA receptor subunit NR1. Antibodies against IL-17 in serum decrease spinal NR1 phosphorylation and hyperalgesia in experimental models.\textsuperscript{49} ATP released from astrocytes might activate P2X3 receptors, which probably adds to the pronociceptive effects of astroglial activation in NMO; glutamatergic transmission at primary afferent nerve fibres is strongly facilitated in spinal cord lamina II by the activation of presynaptic purinergic P2X3 receptors.\textsuperscript{50} Indeed, the pronociceptive effects of P2X3 and certain other purinergic receptors, such as P2X4, P2X7 and P2Y, are well established.\textsuperscript{71,72}

The excitatory actions of glutamate could be potentiated and prolonged by delayed removal of glutamate from the extracellular space, possibly resulting from the reduced expression of EAAT2\textsuperscript{26,37} in NMO lesions. In fact, application of serum from patients with NMO—but not from healthy controls—to rat astrocytes conferred an approximately 50% decrease in glutamate uptake by these cells.\textsuperscript{35,53}

### Table 2 | Inflammatory mediators of nociception

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Evidence for presence in NMO</th>
<th>Evidence for role in pain</th>
</tr>
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<tbody>
<tr>
<td>IL-1β</td>
<td>Higher IL-1β expression levels in macrophages or activated microglial cells contained in early active inflammatory lesions in patients with NMO compared with patients with MS\textsuperscript{45,46}</td>
<td>IL-1β enhances glutamatergic signalling and, thus, enhances the strength of synaptic transmission between nociceptive C fibres (small unmyelinated axons) and spinal lamina I and II neurons\textsuperscript{45}</td>
</tr>
<tr>
<td>IL-6</td>
<td>Detected in the CSF at much higher levels in patients with NMO than in patients with MS\textsuperscript{25,40}</td>
<td>Pronociceptive in rodent models of peripheral\textsuperscript{60} and spinal\textsuperscript{61} forms of neuropathic pain Injection into the CSF induces thermal allodynia in normal rats and increases experimental pain in animals with a previously sensitized spinal cord\textsuperscript{83} Intrathecal administration of neutralizing anti-IL-6 antibodies to rats decreases spinal cord injury-associated mechanical allodynia\textsuperscript{86} Treatment of a single patient with NMO with the anti-IL-6 receptor antibody tocilizumab led to reduced neuropathic pain and disability scores\textsuperscript{64}</td>
</tr>
<tr>
<td>IL-17</td>
<td>Activation of the IL-17–IL-8 axis in the CSF of patients with NMO\textsuperscript{22,47}</td>
<td>Might enhance NMDA receptor-mediated pronociceptive effects in the spinal dorsal horn, as suggested by the phosphorylation of the NMDA receptor subunit NR1 IL-17 antibodies decrease spinal NR1 phosphorylation and hyperalgesia\textsuperscript{49}</td>
</tr>
<tr>
<td>TNF</td>
<td>No evidence for activation of TNF axis in the CSF of patients with NMO\textsuperscript{85}</td>
<td>TNF enhances glutamatergic signalling and enhances the strength of synaptic transmission between nociceptive C fibres and spinal lamina I and II neurons\textsuperscript{45}</td>
</tr>
<tr>
<td>HMGB1</td>
<td>Elevated in the plasma of patients with NMO\textsuperscript{85}</td>
<td>Might facilitate the pronociceptive effects of IL-1β. IL-6 and TNF; since intrathecal injections of a neutralizing HMGB1 antibody blocks the upregulation of these cytokines in the spinal cord in a rodent model of diabetic allodynia\textsuperscript{89}</td>
</tr>
</tbody>
</table>

**Abbreviations:** HMGB1, high mobility group protein B1; MS, multiple sclerosis; NMDA, N-methyl-d-aspartate; NMO, neuromyelitis optica; TNF, tumour necrosis factor.
Excessive levels of extracellular glutamate are toxic to glial cells and neurons. Some inhibitory neurons express Ca\(^{2+}\)-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at relatively high levels, thereby rendering them especially vulnerable to glutamate excitotoxicity. Consequently, these neurons are affected earlier and more strongly than other types of neurons. Glutamate excitotoxicity might, therefore, cause an imbalance between excitation and inhibition in nociceptive pathways, thereby contributing to spontaneous pain, widespread hyperalgesia and allodynia in patients with NMO (Figure 2).

Figure 2 | Stages of neuromyelitis optica lesions and key players and events in the development of pain. a | In early active lesions, long-lasting pain amplification results essentially from the excitatory action and excessive levels of extracellular glutamate. b | In established lesions, loss of astrocytes, which are the almost-exclusive source of glutamine in the CNS, interrupts the glutamine–glutamate–GABA axis, possibly severely disrupting the balance between excitation and inhibition in nociceptive pathways. Segmental and descending inhibition is also impaired.

Abbreviations: AQP4, aquaporin-4; EAAT2, excitatory amino acid transporter 2; GABA, γ-aminobutyric acid; NMDA, \(\text{N}\)-methyl-\(\text{d}\)-aspartate; NMDAR, NMDA receptor; TNF, tumour necrosis factor.
GABA<sub>A</sub> receptors, and glycine, acting on ionotropic glycine receptors, are the main inhibitory neurotransmitters in the nociceptive system. GABAergic and glyciner-gic inhibition serves five essential functions in the nociceptive system (Box 1).

For inhibition exerted via the ionotropic GABA<sub>A</sub> or glycine receptors, an appropriate anion gradient across the cell membrane is essential. The normal anion gradient is, to a large extent, maintained by the neuronal K–Cl cotransporter 2 (KCC2). In NMO, however, appropriate levels of inhibition might be endangered by the release of large amounts of BDNF from activated glial cells or macrophages, as BDNF strongly down-regulates KCC2 expression in laminae I and II neurons. This disruption of inhibitory signalling in the spinal cord affects inhibition of the nociceptive system and might result in spontaneous pain, hyperalgesia and allodynia, widespread pain, and pain chronicity.

Several observations strongly suggest that central disinhibition has an essential role in patients with NMO. First, in one study, 73% of patients with NMO had paradoxical heat sensations; for example, they perceived mild cold stimuli as hot or burning pain. The occurrence of paradoxical heat sensations is promoted by central disinhibition.

Second, astrocytes release the endocannabinoid 2-arachidonoylglycerol (2-AG), which strongly enhances GABAergic inhibition through allosteric modulation of the GABA<sub>A</sub> receptor. Under normal conditions, 2-AG does not cross the blood–brain barrier. However, when the astrocyte destruction seen in patients with NMO impairs astrocyte-mediated control of the blood–brain barrier, or when the blood–brain barrier in these patients is open due to inflammatory processes, the astrocytic 2-AG can be detected in the systemic circulation, where its levels could provide a surrogate marker for its cerebral concentration. High 2-AG concentrations in serum seem to reflect upregulation of 2-AG expression in the CNS as a protective mechanism to promote neuronal survival and might explain the abnormal mechanical hypoalgesia seen in some patients, while the absence of an increase in 2-AG in serum might mirror profound loss of astrocytes in CNS tissue, probably weakening GABAergic inhibition and culminating in hyperalgesia.

Established lesions

The loss of astrocytes in established NMO lesions could further endanger inhibition at the cellular and systemic levels. In the intact CNS, glutamate is taken up by astrocytes, where it is converted into glutamine, a precursor of amino acid neurotransmitters. Glutamine is released from astrocytes and is taken up into neurons by active transport. In GABAergic neurons, glutamine is hydrolysed to glutamate, a portion of which is then decarboxylated to GABA to replenish the synaptic neurotransmitter pools.

Death of astrocytes inevitably interrupts the glutamate–glutamate–GABA pathway, which probably further disturbs the delicate balance of excitation and inhibition in nociceptive pathways.

At the systemic level, NMO lesions might disrupt descending inhibition (Figure 1). Descending antinociceptive pathways (which inhibit pain) originate from various sites in the brainstem, most notably the midbrain periaqueductal grey and the medullary raphe nuclei, and descend via the dorsolateral funiculus to all levels of the spinal cord. In principle, in patients with NMO, descending inhibition, which is indispensable for proper spinal nociception, could be impaired by lesions at the origin of the descending pathways and/or along the descending fibre tracts (Figure 1).

A prominent site of NMO lesions is the midbrain periaqueductal grey, the ventrolateral and dorsal aspects of which provide the source of powerful descending antinociceptive pathways. Descending inhibition is permanently active to maintain physiological levels of nociception, and can be boosted on demand, for example, to mediate stress-induced analgesia in a fight-or-flight situation. One would expect, therefore, that depending on the location within the periaqueductal grey, NMO lesions might seriously impair both tonic and phasic antinociception. This assumption, however, is not supported by available data from patients with NMO. According to a recent multicentre study, symptoms originating in the brainstem, such as hiccups, vomiting, oculomotor dysfunction or pruritus, were seen in approximately 30% of all patients with NMO, but only a small percentage of these patients had lesions in this area that were detectable with conventional imaging techniques. Not all structural changes in brain tissue due to pathology are revealed by MRI, but the frequencies of the visible changes, at least, are in marked contrast to the high numbers of patients with NMO who experience pain.

Hence, lesions at the origin of descending inhibitory pathways probably only have a role in typical NMO neuropathic pain in a subset of patients.

NMO lesions are most frequently found in the grey matter of the cervical spinal cord. Extensive NMO lesions that reach nearby white matter could also affect spinal fibre tracts, including those comprising descending inhibitory pathways. It is highly likely that extensive cervical NMO lesions affect the functioning of descending antinociceptive systems, thereby causing severe spontaneous pain and hyperalgesia at and below the vertebral levels of the lesions.

Recommendations for therapy

Cumulatively, the mechanisms of NMO lesion formation that might relate to pain seem to depend on the stage of the disease. This finding strongly suggests that any mechanism-based form of pain therapy should also be stage-specific.

In patients with early active NMO lesions, pronociceptive effects might result from excess glutamate in the extracellular space, proinflammatory molecules enhancing glutamatergic signalling, and the opening of glutamatergic Ca<sup>2+</sup>-permeable NMDA or AMPA receptors that trigger synaptic LTP. At this early stage of the disease, therapeutic approaches should counteract antibody binding and block or interfere with the cellular and molecular mediators of neuroinflammation and glial activation. Given the complexity of interacting proinflammatory molecules in neuroinflammation, it is highly unlikely that a single target can be identified to eliminate all consequences of
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early NMO lesions. A multidrug treatment, similar to that proposed for traumatic brain injury,\(^6\) might instead be possible. This approach involves minocycline, peroxisome proliferator-activated receptor agonists, cell cycle inhibitors, statins and progerosterone. By contrast, opioids might carry the risk of exacerbating neuroinflammation in an opioid receptor-independent fashion via binding to an accessory protein of Toll-like receptor 4.\(^4\)

Application of pharmaceutical compounds that inhibit glutamatergic signal transduction would also counteract the development of neuropathic pain. A number of drugs that are used clinically interfere directly with glutamate receptors and could potentially alleviate pain in patients with NMO. Activation of NMDA receptors can trigger LTP and excitotoxicity, which can be blocked by low-dose ketamine or by memantine. Recently, the therapeutic potential of modulation of AMPA receptors has been explored, and the results suggest that AMPA receptor antagonists such as NGX426 might be effective.\(^7\)

Finally, antagonists of group I metabotropic glutamate receptors (mGluRs) are being studied preclinically or in clinical trials to explore their therapeutic potential, largely for mood disorders. Animal experiments suggest that these agonists might also have beneficial effects in treating neuroinflammation, given the expression of mGluRs not only on neurons, but also on microglia and astroglia.\(^8\) Experimental preclinical data suggest that selected patients might benefit from the erasure of spinal memory traces of pain after the initial inflammatory process.\(^9\) In animal models, pain memory erasure is achieved by reverberation of the underlying mechanisms of pain in individual patients with NMO, and could provide the basis for personalized analgesic therapy.

First future research directions

The development of satisfactory pain management in patients with NMO crucially relies on major improvements in several areas. First, abnormalities of somatosensory function should be routinely assessed in each patent, for example, by quantitative sensory testing.\(^10\) Second, these abnormalities should be related to the exact anatomical site of the lesions and to the stage of the disease, and these parameters should all be closely monitored over time. Such assessments could contribute to the identification of the underlying mechanisms of pain in individual patients with NMO, and could provide the basis for personalized analgesic therapy.

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Acknowledgments

We thank Takashi Yamamura for being the first to call our attention to the connection between neuromyelitis optica and pain. Our work is supported by the Austrian Science Fund (grant numbers P25240-B24 to M.B., I916-B13 [International Programme, Eugène Devic European Network] to H.L. and P22306-B19 to J.S.), and in part by the Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Technology and the Ministry of Health, Labor and Welfare of Japan to K.F.

Author contributions

All authors researched data for the article, and contributed to discussion of content and review/editing of the manuscript before submission. M.B., H.L. and J.S. wrote the article.