Immunotherapy-Responsive Neuropathic Pain and Allodynia in a Patient With Glycine Receptor Autoantibodies

A Case Report

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Abstract

Objectives
Neuropathic pain is common and distressing. Improved mechanistic understanding and pharmacotherapies are urgently needed. Molecularly specific pain syndromes may provide insights with translational relevance. Glycine receptors are known to play a key role in inhibitory neurotransmission in the spinal dorsal horn and have therefore been considered as targets for analgesic development. While autoantibodies directed against glycine receptors may rarely arise spontaneously in humans, a detailed phenotype of neuropathic pain and allodynia in association with these autoantibodies has not been described.

Methods
We describe the case of a previously well adult presenting with severe neuropathic pain and allodynia as part of an autoimmune brainstem and spinal syndrome with glycine receptor autoantibodies.

Results
Our patient experienced a severe illness, including marked neuropathic pain and allodynia, hypoventilation, tetraparesis, and ophthalmoplegia. A diagnosis of progressive encephalomyelitis with rigidity and myoclonus was made. Neuropathic pain was characterized with validated instruments and responded promptly to cause-directed immunotherapy.

Discussion
A detailed longitudinal phenotyping, using validated pain measurement instruments, of severe neuropathic pain and allodynia associated with likely pathogenic glycine receptor autoantibodies is reported. This case may have relevance for translational development of analgesics targeting glycnergic neurotransmission.

Background
Neuropathic pain is frequently a feature of disorders of the peripheral and central nervous systems; however, effective therapies are limited and are often associated with significant side effects.1 A subset of human neuropathic pain conditions mediated by pathologic...
immunoglobulin G (IgG) autoantibodies\textsuperscript{2,3} may allow improved mechanistic understanding of human pain processing and aid analgesic development.

Opioids, noradrenaline, and serotonin play key roles in CNS pain processing and are targeted by many current pharmacologic analgesia strategies.\textsuperscript{1} However, glycinergic neurotransmission has fairly recently been established in preclinical models to play an important role in pain and hyperalgesia,\textsuperscript{4} likely because of the role of glycine (along with gamma amino-butyric acid) in fast inhibitory pathways.\textsuperscript{4} In animal models, reduction of inhibitory glycinergic neurotransmission has been found to lead to allodynia, itch and pain; whereas activation of glycinergic pathways has been found to reduce pain and hyperalgesia.\textsuperscript{4,5} Despite these findings, no glycine receptor modulators are approved for human use,\textsuperscript{6} and side-effect profiles in humans have not been characterized.\textsuperscript{7}

Pathogenic autoantibodies may rarely spontaneously arise against the extracellular domains of human glycine receptors (GlyR)\textsuperscript{2} and are most consistently associated with progressive encephalomyelitis with rigidity and myoclonus (PERM) and stiff-person syndrome.\textsuperscript{2,8,9} Although pain has been described in patients with PERM, it is often related to muscular spasms.\textsuperscript{8} No previous reports have fully characterized neuropathic pain and allodynia in association with autoantibodies against GlyR in humans.\textsuperscript{2,8} Here, we report severe neuropathic pain and allodynia in association with GlyR autoantibodies, along with response to immunotherapy, using validated instruments.

**Case Report**

A 33-year-old woman was referred to neurology services for assessment of mild recent sensory disturbance and difficulty walking, which had begun 2 months previously. Her medical history was of well-controlled asthma. Family history was unremarkable. Initial symptoms had been of paresthesia and numbness of her right face and left leg. Despite resolution of facial symptoms, the left leg was described as “painful and numb” with variable subjective stiffness and weakness.

Over 6 months, sensory features spread to involve both lower limbs, and she additionally developed symptoms of stiffness and tightness around the trunk and abdomen. No pathologic muscle contraction was clinically apparent.

Unfortunately, approximately 8 months after symptom onset, her mobility deteriorated markedly, requiring hospital admission. On assessment, a mix of brainstem and spinal features were noted. There was a complex ophthalmoplegia, tetraparesis, hyper-reflexia with extensor plantars, clonus at the ankles and knees, and urinary retention requiring catheterization. She required a hoist to transfer. She was not encephalopathic. She developed nocturnal apneic episodes due to central hypoventilation and extensor spasms of the lower limbs.

Simultaneously, she developed worsening severe neuropathic pain that was constant and described as “electric shocks”

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**Figure 1** Reactivity of Patient Serum Against the Extracellular Domains of Glycine Receptors Expressed in Live HEK293T Cells

IgG reactivity of patient serum against HEK293T cells transfected to express surface glycine receptors (alpha-1 subunit; fused with EGFP, green) and incubated with patient serum (IgG detection in red). Reactivity was observed visually after incubation with patient serum (panel B.b), but not healthy control serum (panel A.b). Merged images show DAPI, identifying cell nuclei. Scale bar denotes 15 μm. GlyR = glycine receptor; EGFP = enhanced green fluorescent protein; DAPI = (4',6-diamidino-2-phenylindole).
throughout both lower limbs and abdomen. Marked mechanical allodynia was noted, with light touch described as “excruciating” and “like electric barbed wire.” Neuropathic pain was described by the patient in a similar distribution to pre-existing sensory disturbance. She separately experienced episodic non-neuropathic pain related to spasms.

**Diagnostic Evaluation**

A range of serologic and CSF investigations as well as serial MRI of brain and spine were performed (additional data are listed in eTable 1, links.lww.com/NXI/A895). CSF demonstrated oligoclonal bands isolated to the CNS compartment. Nerve conduction studies, and EMG during subjective spasm, were normal. Clinical and radiologic assessment identified no underlying malignancy. Somatosensory evoked potentials were not available for technical reasons.

At 8 months after symptom onset, autoantibodies directed against GlyRs were identified in both serum and CSF, confirming a clinical diagnosis of PERM. Testing for other autoantibodies associated with pain syndromes was negative (eTable 1, links.lww.com/NXI/A895).

IgG reactivity against GlyRs was determined as previously described\(^8\) using HEK293T cells transfected to express surface GlyRs (alpha-1 subunit). After surface expression of GlyRs, these cells were incubated with patient serum or CSF. Binding of human IgG to these cells, but not untransfected cells, was observed visually and titrated to end point dilutions of 1:2,500 (serum) and 1:50 (CSF) (Figure 1).

**Characterization of Pain Phenotype**

The patient completed questionnaires to characterize her pain syndrome and treatment response. PainDetect\(^10\), McGill Pain Questionnaire\(^11\), and body maps (front and back) demonstrating location of neuropathic pain, and, separately, nonpainful sensory disturbance\(^10\) were completed. Free-text comments were recorded contemporaneously. Questionnaires were completed at 8, 9, and 13 months after symptom onset (immediately before commencing immunotherapy, 1 month, and then 5 months after immunotherapy, respectively) (Figure 2, Table 1).

**Clinical Progress**

On initial suspicion of GlyR autoantibody-mediated syndrome, aggressive immunotherapy comprising high-dose IV steroids and plasma exchange was instituted (8 months after symptom onset). This immunotherapy was associated with a marked improvement in pain within 48–72 hours (Figure 2, Table 1). In addition, there was rapid resolution of ophthalmoplegia and apneic episodes and attainment of full independent mobility. A tapering dose of oral steroids was maintained. Rituximab was started 4 months thereafter as maintenance therapy (2 1 g doses separated by one fortnight, then 1 g 6-monthly), allowing steroid cessation. IV immunoglobulin was not administered. The patient remains fully

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**Figure 2 Patient-Reported Distribution of Nonpainful Neuropathic Sensory Symptoms and Neuropathic Pain**

<table>
<thead>
<tr>
<th>Time since symptom onset</th>
<th>8 Months</th>
<th>9 Months</th>
<th>13 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since immunotherapy</td>
<td>N/A</td>
<td>1 Month</td>
<td>5 Months</td>
</tr>
<tr>
<td>Nonpainful sensory symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Front</td>
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<tr>
<td>Back</td>
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<td><img src="image" alt="Back" /></td>
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<tr>
<td>Neuropathic pain</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Front</td>
<td><img src="image" alt="Front" /></td>
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Our patient hand-drew location of symptoms on body silhouettes at 3 time points (paper copy, separately at 8, 9, and 13 months since symptom onset). Separate body silhouettes were provided representing the front and back of body. At each time point, the distribution of nonpainful sensory symptoms, and of neuropathic pain, were marked separately. Shading denotes location of symptoms at each time point. Absence of shading denotes absence of symptoms.
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Abbreviation: MPQ = McGill Pain Questionnaire.

Table 1 Pain Severity and Phenotype Before and After Institution of Immunotherapy

<table>
<thead>
<tr>
<th>Time point</th>
<th>Pain detect “average pain in last 4 wk” (range 0–10)</th>
<th>Pain detect sum score (range 0–38)</th>
<th>MPQ sum score (range 0–78)</th>
<th>MPQ “pain right now” (range 0–5) (text descriptor included in MPQ instrument)</th>
<th>MPQ “pain at its worst” (range 0–5) (text descriptor included in MPQ instrument)</th>
<th>MPQ “pain at its least” (range 0–5) (text descriptor included in MPQ instrument)</th>
<th>Free-text pain descriptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mo since symptom onset (before immunotherapy)</td>
<td>10</td>
<td>37</td>
<td>69</td>
<td>5 (excruciating)</td>
<td>5 (excruciating)</td>
<td>5 (excruciating)</td>
<td>“Like electric shocks” “constant”</td>
</tr>
<tr>
<td>9 mo since symptoms onset (1 mo after immunotherapy instituted)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (absent)</td>
<td>0 (absent)</td>
<td>0 (absent)</td>
<td>“None of the questions feel relevant as I don’t have pain” Not requiring any analgesia</td>
</tr>
<tr>
<td>13 mo since symptom onset (5 mo after immunotherapy instituted)</td>
<td>3</td>
<td>5</td>
<td>36</td>
<td>1 (mild)</td>
<td>2 (discomforting)</td>
<td>1 (mild)</td>
<td>“Slightly strong but manageable”</td>
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</table>

Pain Severity and Phenotype Before and After Institution of Immunotherapy

The clinical data described allow a definite clinical diagnosis of neuropathic pain.13 Furthermore, a PainDetect score of 37 (preimmunotherapy; range 0–38) is in keeping with neuropathic pain (highly likely at scores ≥19).10 Neuropathic pain syndromes are increasingly reported in antibody-mediated disorders affecting central or peripheral nervous systems.2 Clinical assessment strongly favored a CNS etiology, and we believed that investigation for concurrent small fiber neuropathy was not indicated. Our case description may aid diagnostic evaluation of patients with suspected autoantibody-mediated syndromes, in the context of appropriate clinical and investigation findings.3,8

Future studies could further investigate the possibility of neuropathic pain associated with GlyR autoantibodies.

Glycine predominantly mediates inhibitory neurotransmission through its receptor, a chloride channel, leading to hyperpolarisation and reduced excitation.14 GlyRs are most abundant in the dorsal horn of the spinal cord where they play a role in inhibiting nociceptive transmission.14 Autoimmunity against GlyR is strongly associated with brainstem and spinal cord hyperexcitability disorders.15 The mechanism by which autoantibodies against GlyRs act in vivo is not known. In vitro, patient autoantibodies have been shown to lead to internalization and lysosomal degradation of GlyRs.8 Other mechanisms of action might include direct inhibition of GlyR function,15 as perhaps supported by rapid treatment response in this case.

While no GlyR modulators are approved for human use,6 glycinergic neurotransmission has attracted attention as a possible target of translational analgesic development.7,12

This case suggests that glycinergic neurotransmission may contribute to modulation of neuropathic pain, and allodynia, in humans. However, other manifestations described here, including impaired respiratory control and increased muscle tone, echo additional known physiologic roles of GlyRs.7 Future development of analgesics targeting glycinergic neurotransmission should therefore carefully consider potential effects outside pain pathways.7

Discussion

We describe a case of severe, immunotherapy-responsive, neuropathic pain and allodynia, associated with autoantibodies against GlyR. PERM and related disorders have been described to cause spasm-related pain, and separately non-spasmodic pain in approximately one in 5 patients.8 No previous report has described definite neuropathic pain nor used validated pain outcome measures.”2,8,9 Although we cannot exclude a role of an additional unidentified autoantibody, we prefer direct pathogenicity as an explanation because of close recapitulation of phenotypes in preclinical models,4,5,12 binding of autoantibodies to extracellular domain of GlyR (confirming pathogenic potential) (Figure 1) and negative testing for other IgG autoantibodies related to pain syndromes (eTable 1, links.lww.com/NXI/A895).

The clinical data described allow a definite clinical diagnosis of neuropathic pain.13 Furthermore, a PainDetect score of 37 (preimmunotherapy; range 0–38) is in keeping with neuropathic pain (highly likely at scores ≥19).10 Neuropathic pain syndromes are increasingly reported in antibody-mediated disorders affecting central or peripheral nervous systems.2 Clinical assessment strongly favored a CNS etiology, and we believed that investigation for concurrent small fiber neuropathy was not indicated. Our case description may aid diagnostic evaluation of patients with suspected autoantibody-mediated syndromes, in the context of appropriate clinical and investigation findings.3,8

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References