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【 CASE REPORT 】

Complete Relief of Painful Tonic Seizures in Neuromyelitis Optica Spectrum Disorder by Satralizumab Treatment

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Abstract:
Satralizumab, a monoclonal antibody against interleukin-6 receptors, has been approved for the treatment of neuromyelitis optica spectrum disorder (NMOSD). Several reports have described the effectiveness of satralizumab against neuropathic pain in patients with NMOSD, but its effects on painful tonic seizures have not yet been reported. We herein report a Japanese woman with anti-aquaporin-4 antibody-positive NMOSD whose painful tonic seizures completely resolved after six months of satralizumab treatment. In conclusion, interleukin-6 blocking may be effective against painful tonic seizures. This effect may be due to suppression of microglial activation and the resultant neuronal hyperexcitability.

Key words: IL-6, neuromyelitis optica, painful tonic seizures, satralizumab

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Introduction

Neuromyelitis optica (NMO) spectrum disorder (NMOSD) is an inflammatory disorder of the central nervous system in which anti-aquaporin-4 (AQP4) antibodies mainly affect the optic nerves, spinal cord, and brainstem (1). Interleukin-6 (IL-6) has a wide range of biological functions, including B cell stimulation and T cell activation. Elevated serum and cerebrospinal fluid (CSF) levels of IL-6 have been reported in NMO (2), which suggests that IL-6 plays an important role in the pathogenesis of NMO: IL-6 facilitates the survival of plasmablasts and promotes the production of anti-AQP4 antibodies from plasmablasts (3); is involved in blood-brain barrier disruption (4); and is correlated with astrocytic damage and inflammation (2). Treatment with humanized anti-IL-6 receptor antibodies (tocilizumab or satralizumab) significantly decreases the annualized relapse rate, the Expanded Disability Status Scale score, neuropathic pain, and general fatigue in NMOSD patients (5-7).

We herein report a patient with NMOSD whose painful tonic seizures were completely alleviated after six months of satralizumab treatment.

Case Report

A 35-year-old Japanese woman experienced 5 inflammatory episodes over 3 years. When she was 32 years old, she suffered an extensive spinal cord lesion (Th2-7) and was diagnosed with NMOSD based on serum anti-AQP4 antibody positivity. At 33, she suffered a third ventricle lesion and left optic nerve lesion. At 34, she experienced a right optic nerve lesion and C2-3 cervical lesion involving the dorsal column of the spinal cord (Fig. 1). At the episode of cervical myelitis, neurological examinations revealed no weakness, diminished sensations to pain and vibration at the bilateral upper limbs, allodynia at the left neck to the upper left limb, and urinary dysfunction. At approximately one month after the myelitis onset, she developed frequent (once an hour, visual analog scale 10) painful tonic seizure of left upper limb.

Acute treatment with high doses of intravenous methylprednisolone and plasmapheresis was administered for each of her NMOSD relapses. Despite ongoing treatment with prednisolone (15-30 mg/day) and azathioprine (50-100 mg/day), the patient suffered frequent relapses. Therefore, we administered satralizumab, which prevented relapses for the

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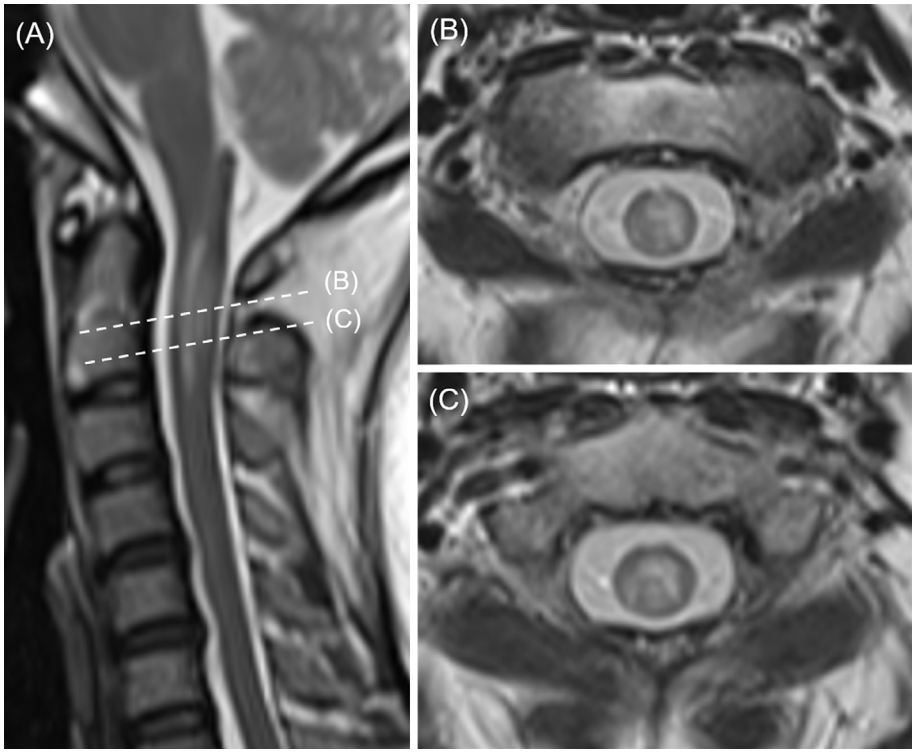

Figure 1. **Spinal cord magnetic resonance imaging at the inflammatory episode of cervical myelitis. Sagittal (A) and axial (B, C) images on T2-weighted imaging of the cervical spinal cord showed a C2-3 lesion. The C2 lesion involved the dorsal column of the spinal cord (left side dominant).**

next 12 months (annualized relapse rate was reduced from 2.3 to 0 times/year). As described above, the patient suffered from painful tonic seizures of left upper limb after cervical myelitis at 34 years old. Treatment with carbamazepine, clonazepam, and gabapentin failed to suppress these seizures. However, satralizumab therapy dramatically alleviated her painful tonic seizures (both the frequency and degree of pain), resulting in their complete resolution six months after the start of satralizumab therapy (Fig. 2).

Discussion

We described a patient with NMOSD whose frequent relapses and intractable painful tonic seizures were completely resolved after satralizumab treatment. Anti-IL-6 receptor antibody therapy (satralizumab and tocilizumab) significantly reduces NMOSD relapses (5-7), and several studies have reported that IL-6 blockade can also suppress pain in NMOSD (5, 6).

There is evidence of a relationship between spinal microglia and neuropathic pain. Neurological injury causes the activation of microglia, which increases P2X4 expression and releases brain-derived neurotrophic factor. This, in turn, causes dysfunction of gamma-aminobutyric acid inhibitory neurons, resulting in pain hypersensitivity due to the promotion of excitatory synaptic transmission in neurons of the dorsal spinal cord (8). Anti-IL-6 receptor antibodies were found to reduce sensitivity to pain and decrease mechanical allodynia in experimental autoimmune encephalomyelitis mice through the inhibition of microglial activation and proliferation in the spinal cord (9).

Conversely, no correlation has been found between serum IL-6 levels and scores on the Pain Effects Scale (10), and satralizumab failed to reduce pain scores in a clinical trial (7). A possible explanation for these conflicting findings is that not all participants in the trial suffered pain or had spinal cord lesions.

Painful tonic seizures are paroxysmal episodes of increased muscle tone, abnormal posture, and intense pain in one or more limbs. These are sometimes triggered by movement or sensory stimulation. Painful tonic seizures are a relatively common symptom of NMOSD. They are caused by lesions at the dorsal column of the spinal cord, which lead to the abnormal excitation of neuronal axons. To our knowledge, no previous study has evaluated the effects of satralizumab on painful tonic seizures. We speculate that painful tonic seizures result from the same mechanism as neuropathic pain and believe that IL-6 blocking by satralizumab suppress microglial activation and the resultant neuronal hyperexcitability; thus, it may be effective for painful tonic seizures, which are caused by abnormal excitation of neuronal axons due to lesions at the dorsal column of the spinal cord.

Conclusion

We reported the first case of a patient with NMOSD whose painful tonic seizures were completely resolved by satralizumab. IL-6 blockade therapy may be an effective

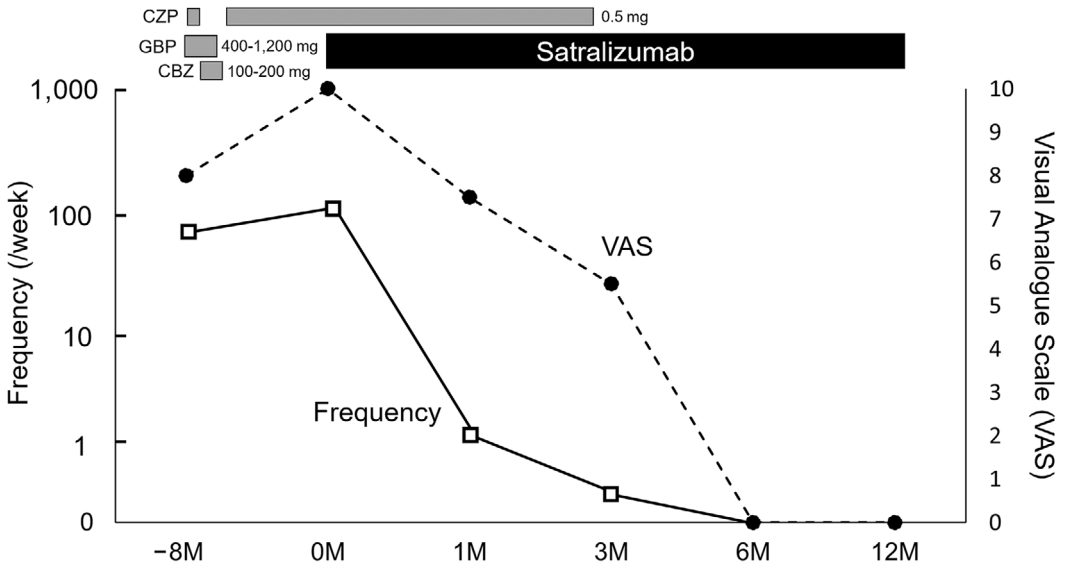

Figure 2. **Time course of painful tonic seizures after satralizumab treatment. Her painful tonic seizure started approximately one month after the onset of myelitis. The patient suffered painful tonic seizures for eight months. Treatment with carbamazepine (CBZ), clonazepam (CZP), and gabapentin (GBP) failed to suppress painful tonic seizures. Before satralizumab treatment, painful tonic seizures occurred once an hour [visual analog scale (VAS) 10]. After one month of treatment, the seizures were reduced to once a week (VAS 7.5). After three months of treatment, seizures were reduced to once a month (VAS 5.5). After six months of satralizumab treatment, the seizures disappeared.**

treatment for pain and painful tonic seizures in NMOSD, although further systematic research is required.

The patient gave her informed consent to publish the clinical data in an anonymized form.

The authors state that they have no Conflict of Interest (COI).

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