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# Application of immunotherapy for neurological manifestations in hypermobile Ehlers–Danlos syndrome

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***Abstract:*** Ehlers–Danlos syndrome (EDS) is a heterogeneous heritable connective tissue disorder with various neurological manifestations, including chronic pain. The neurological manifestations in EDS are often regarded as being caused by the associated musculoskeletal disorders or polyneuropathy. Here, we present two patients with hypermobile EDS (hEDS), presenting with relapsing central nervous system (CNS) manifestations. Although the two patients showed relapsing signs of CNS manifestations like multiple sclerosis (MS) or *neuromyelitis optica* spectrum disorder (NMOSD), they were unique in that they had widespread opioid-dependent chronic pain, which is not consistent with the symptoms of MS/NMOSD. Unexpectedly, the serious pain of unknown origin was remarkably mitigated by plasmapheresis, and magnetic resonance imaging (MRI) examinations conducted for one of the patients were negative. Collectively, we speculate that hEDS may be more susceptible to 'normal-appearing imaging, neuroimmunologically justified, autoimmune-mediated encephalomyelitis (NINJA).' Analysis of the presented cases and an additional three patients with EDS with chronic pain indicates that treatable immune-mediated mechanisms deserve considerations for neurological symptoms observed in hEDS.

***Keywords:*** hypermobile Ehlers–Danlos syndrome, immunotherapy, neurological manifestations, neuropathic pain, plasmapheresis

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## Introduction

The Ehlers–Danlos syndromes (EDS) are a heterogeneous group of hereditary connective tissue disorders preferentially characterized by joint hypermobility, skin hyperextensibility, and tissue fragility. Patients with EDS are currently classified into 13 subtypes.[1] Mutations in collagen type V genes (*COL5A1, COL5A2*) are reported to cause the classical EDSs; *COL3A1*, vascular EDS; genes encoding extracellular matrix proteins, other rare EDSs; and transforming growth factor beta superfamily (*TGFBR1/2* and *SMAD3*), a pathogenic variant of EDS.[2] In contrast to these subtypes, the molecular basis of hypermobile EDS (hEDS) remains to be identified.

Of note, neurological symptoms are frequently observed in EDS,[3] and are commonly attributed to the associated musculoskeletal disorders or polyneuropathy,[4] unless coexistence of CNS diseases such as multiple sclerosis (MS) is identified.[5] Chronic pain is a common manifestation of EDS and more frequent in patients with hEDS.[6] Here, we present two cases of hEDS with the following relapsing neurological manifestations: paraplegia, visual impairment, diplopia, and intractable nausea and vomiting. Despite the provisional diagnosis of MS or seronegative *neuromyelitis optica* spectrum disorder (NMOSD), these were not regarded NMOSD cases, as the chronic pain was widespread and neurological paralysis and pain reversibility was higher than achieved after plasmapheresis. Based on the clinical course and measurement of plasmablasts in the peripheral blood, we speculate that the clinical features of these patients resemble those of 'normal-appearing

imaging, neuroimmunologically justified, autoimmune-mediated encephalomyelitis (NINJA).' We indicate that intractable chronic pain in hEDS should be regarded as immune-mediated pain and immunotherapy be provided.

## Methods

The Ethics Committee of the National Center of Neurology and Psychiatry on human experimentation approved the present study (approval number: A2014-082), which conformed to the tenets of the Declaration of Helsinki. Written informed consent for the publication of patient information was obtained from all participants. The plasmablast frequency ($CD19^{+}CD27^{high}CD38^{high}CD180^{-}$ cells) was measured using flow cytometry (FACS Canto II, BD Biosciences, San Jose, CA, USA) and defined as the proportions (%) of $CD19^{+}$ cells among peripheral blood mononuclear cells, as described previously.[7]

## Case reports

Case 1: the patient was a 41-year-old homemaker. She had noticed joint hypermobility and had experienced pain since a young age. She had shoulder and finger subluxation since the age of 6 years. Cardiac ablation was performed for supraventricular tachycardia at the age of 24 years, and pacemaker implantation for bradycardia at the age of 28 years. She was initially diagnosed with vascular EDS (vEDS) at the age of 29 years, because a skin biopsy revealed low levels of collagen type III. However, since no known genetic basis was identified,[1] she was diagnosed with hEDS at the age of 34 years by EDS experts, based on the clinical criteria.[1] There was no family history of EDS. Opioids were initiated at the age 30 years for intractable chronic pain, which had been widespread and uncontrollable.

Her first neurological symptom, except for chronic pain, was paraplegia, which occurred at the age of 22 years. Although slow paced, the recovery from the paraplegia was almost complete within 1 year, and she entered a state of remission. Subsequently, she experienced a few relapses, which were thought to support the diagnosis MS or NMOSD (MS/NMOSD). She was diagnosed with MS/NMOSD during the third paraplegia attack at the age of 34 years. Brain and spinal cord magnetic resonance imaging (MRI) studies were not conducted owing to pacemaker implantation. Computed tomography showed neither spinal cord atrophy nor spinal diseases including atlantoaxial instability. Based on the clinical diagnosis of MS/NMOSD, oral prednisolone was initiated, but she experienced several attacks of paraplegia, visual impairment, and dysphagia under the treatment, with an interval ranging from a few to several months. At the age of 36 years, she had severe nausea, vomiting, and dizziness, which were resistant to corticosteroid therapy, and was admitted to our hospital. Objective neurological findings on admission were as follows: left horizontal nystagmus, diplopia, entire muscle weakness of extremities and trunk, distal hypoesthesia of extremities, hyper-reflexia of the upper and lower limbs, bilateral finger flexor and left extensor plantar reflex, and urinary retention. She was bedridden due to severe dizziness, which was resistant to several courses of intravenous methylprednisolone (IVMP). None of the following autoantibodies (auto-Abs) were detected in the patient's sera: antiaquaporin 4 (AQP4) Ab; antimyelin-oligodendrocyte glycoprotein (MOG) Ab; antinuclear antibody (ANA); anti-Ro/SSA Ab; anti-La/SSB Ab; antithyroid Ab. AQP4 and MOG Abs were examined using a cell-based assay. Cerebrospinal fluid (CSF) exhibited neither pleocytosis nor elevated protein levels. The immunoglobulin G (IgG) index was within normal limits and oligoclonal bands were not found. Nerve conduction study was normal. However, prolonged visual evoked potential (P100: 152.1 ms, bilateral flash) and I–V interpeak intervals of auditory brainstem responses (right: 4.7 ms; left: 4.5 ms) were suggestive of CNS demyelination. Sequential treatment with seven courses of immunoadsorption plasmapheresis (IAPP) followed by high-dose intravenous Ig (400 mg/kg/day for 3 days) had an obvious effect on the refractory neurological symptoms. Of note, chronic neuropathic pain of the lower limbs and trunk, which had persisted for more than 6 years, was greatly mitigated after IAPP or plasma exchange (PLEX), which resulted in the discontinuation of oral opioid and tapered opioid plaster. She experienced neurological exacerbations at 1.5, 4, and 5 years after first admission, but improved with IAPP or PLEX on all occasions.

Case 2: the patient was a 42-year-old female office worker. She had noticed joint hypermobility since a young age. Her eldest sister had died of brainstem hemorrhage at the age of 32 years; the precise etiology was not confirmed. She had repeated dislocations and meniscal tears since adolescence.

**Table 1.** Demographics of five patients with hypermobile Ehlers–Danlos syndrome.

| Case | Age (years) | Sex | Allergy | Neurological manifestations | Immune disease | Immunotherapy | Plasmablast (cut-off value: 3.9%) |
|---|---|---|---|---|---|---|---|
| 1 | 41 | F | Drug+ | Visual impairment<br>Nausea and vomiting<br>Dizziness<br>Chronic pain<br>Dystonia | – | PSL + TAC | 4.5 |
| 2 | 42 | F | Drug+<br>Food+<br>Metal+ | Visual impairment<br>Diplopia<br>Headache<br>Nausea and hiccup<br>Chronic pain | Idiopathic hypogammaglobulinemia | PSL + TAC<br>Periodic IVIg | 5.1 |
| 3 | 44 | F | Food+ | Chronic pain | Spondylarthritis | PSL + MTX | 4.0 |
| 4 | 23 | F | | Chronic pain<br>Monoparesis | Behcet's disease,<br>Congenital immunodeficiency | Periodic IVIg | 6.5 |
| 5 | 27 | F | Pollen+ | Chronic pain | – | – | 1.0 |

IVIg, intravenous immunoglobulin; MTX, methotrexate; PSL, prednisolone; TAC, tacrolimus.

During operations, at the age of 16, 20, and 24 years, anesthetic agent-induced anaphylactic shocks had occurred. She also showed allergies to nonsteroidal anti-inflammatory drugs, pilins, antibiotics, and gel patches, food (melon, mango, and peach), and metals (silver and gold plating). She was suspected to have EDS based on a comorbid molluscoid pseudotumor in her lumbar region; however, no clear EDS family history or known genetic abnormalities were revealed. Based on clinical characteristics that met the major criteria of hEDS, she was diagnosed with hEDS at the age of 24 years. Opioids were initiated at the age of 36 years for refractory chronic pain, for which no causal lesion was identified.

Intractable vomiting and hiccups had often occurred since the age of 34 years. Visual impairment and diplopia at the age of 36 years were the first neurological manifestations. She received a single course of IVMP, resulting in the improvement of symptoms. Oral corticosteroid and tacrolimus were administered to prevent the attack. Loxoprofen for chronic pain could be discontinued under the treatment of steroid and immunosuppressant. Her second attack occurred at the age of 41 years. Due to severe visual impairment and diplopia resistant to two courses of IVMP, she was admitted to our hospital for further treatment. Her neurological findings were as follows: decreased visual acuity, diplopia, distal muscle weakness, hyperreflexia, and spasticity of lower limbs, hypoesthesia on the foot in the L5 dermatome and further, and decreased deep sensation of the lower limbs. Brain and spinal cord MRI showed neither demyelinating lesions nor spinal diseases. None of the following auto-Abs were detected in the patient's serum: anti-AQP4 Ab; anti-MOG Ab; ANA; anti-Ro/SSA Ab; anti-La/SSB Ab; antithyroid Ab. CSF and visual evoked potential (VEP) were not tested as per her request. She received seven courses of IAPP, which resulted in improvement of the visual disturbances. Furthermore, her intractable chronic pain also improved after plasmapheresis; the numerical rating score (NRS) of 6 before IAPP reduced to 3 after IAPP.

We further investigated the clinical histories and immunological analysis of a series of five patients with hEDS, including the presented cases (Table 1). Allergy to drugs, foods, and metals was identified in four patients (patient 1, 2, 3, and 5). In addition to the present cases (patient 1 and 2), patient 3 and 4 also had comorbid hEDS and other autoimmune diseases. The four patients with autoimmune diseases showed a high

frequency of plasmablasts, which has the potential to produce pathogenic autoantibodies.

## Discussion

The two patients with hEDS showed MS/NMOSD-like CNS manifestations that were responsive to corticosteroid and plasmapheresis treatment. They may correspond to a clinical category of NINJA[8] although other possibilities remain. Notably, four EDS patients were identified among 1892 patients with MS in a previous study.[5] The authors argued that an increased prevalence of EDS in MS was suggestive of a possible causal relationship in terms of a connective-tissue-level abnormality leading to a higher susceptibility of MS. We noted two major clinical dissimilarities on comparing the CNS manifestations in the present cases with those in patients with MS/NMOSD. Firstly, the paraplegia in the two patients was much more reversible than expected, compared with the 600 MS/NMOSD patients previously treated at our hospital. In general, if paraplegia or tetraplegia reoccurs in MS/NMOSD patients, the usual outcome is severe physical impediment such as a wheelchair-bound or bedridden state. However, although both patient 1 and 2 had entered the bedridden state following a severe attack, they gradually improved after immunotherapy, and were eventually able to walk without any assistance. Secondly, the distribution and characteristics of chronic pain was different between the two EDS cases and MS/NMOSD. In MS/NMOSD, the patients experience girdle sensation and neuropathic pain in the extremities, which is attributed to spinal dermatome. In contrast, the chronic pain in our EDS patients was not localized but widespread. Furthermore, although chronic pain tends to be refractory to pain medications or immunotherapy in MS/NMOSD, chronic widespread pain in case 1 dramatically mitigated after plasmapheresis. A satisfactory reduction of chronic pain after plasmapheresis was also observed in case 2.

It has recently been proposed that the diverse clinical features of EDS, including neurological and immunological manifestations, can be attributed to mast cell activation.[9,10] Roles of mast cells have also been indicated in the pathogenesis of autoimmune diseases, MS, and rheumatoid arthritis.[11] On the other hand, elevated basal serum tryptase levels have been exclusively associated with duplication of the *TPSAB1* gene encoding α-tryptase, followed by mast cell activation.[12] In both the present cases, serum tryptase levels were normal, with the blood samples obtained not in the exacerbation but in the remission phase.

These case reports and case series suggest that the pathogenesis of hEDS can be partly associated with an autoimmune mechanism. While the underlying mechanisms of hEDS remain unclear, autoimmunity and mast cell activation may play key roles. Further clinical investigations are needed to elucidate how autoimmune mechanisms influence the pathogenesis of hEDS and evaluate the efficacy of immunotherapy.

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## Author contributions

Study concept and design: MA, LY, TY; data acquisition and analysis: HO, WS; drafting and revising the manuscript: MA, TY.

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## Conflict of interest statement

The authors declare that there is no conflict of interest.

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