Demyelinating Neuropathy with Markedly Elevated Serum IgG4 Levels and Anti-Contactin 1 IgG4 Antibody

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Abstract:
We herein report a 77-year-old man with a 4-month history of progressive gait and sensory disturbances of the extremities. A nerve conduction study indicated demyelinating polyneuropathy. Serum IgG4 levels and anti-contactin 1 IgG4 antibodies were markedly increased. The sural nerve biopsy specimen showed IgG4-positive plasma cell infiltration in the epineurium. Treatment with steroids resulted in an amelioration of functional status, improvement of nerve conduction parameters, decreased serum IgG4 levels, and negative conversion of anti-contactin 1 antibody. Further studies are needed to clarify the significance of IgG4-positive plasma cell infiltration in anti-contactin 1 antibody-positive neuropathies.

Key words: Chronic inflammatory demyelinating polyneuropathy, contactin 1, intravenous immunoglobulin therapy, steroid therapy

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Introduction
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated, chronic relapsing or progressive neuropathy with varied clinical manifestations (1). Recently, autoantibodies against adhesion molecules in the paranodal area, such as neurofascin-155 (NF155) and contactin 1 (CNTN1), have been detected in some patients with CIDP, and their IgG subclass is reported to be predominantly IgG4 (2, 3). However, the titers of pathogenic autoantibodies are usually very low, and serum IgG4 levels are not elevated.

We herein report a case of demyelinating neuropathy with markedly elevated serum IgG4 levels and anti-CNTN1 IgG4 antibody.

Case Report
A 77-year-old man visited the hospital with progressive numbness of the lower limbs and gait disturbance for 4 months. He had no relevant family history but had received treatment for diffuse large B-cell lymphoma and type 2 diabetes for seven years with metformin hydrochloride, vildagliptin, and glimepiride treatment. His HbA1c was 8.5% at his visit. The lymphoma had been in remission for four years.

He was unable to walk at the time of hospitalization. His tactile, vibratory sensation and positional perception were markedly diminished distal to the elbow and knee. Deep tendon reflexes were generally absent in the extremities, and Romberg’s sign was positive. No tremor or autonomic or cranial nerve symptoms were observed, but mild muscle weakness and pseudoathetosis were noted in the distal extremities.

Serum soluble interleukin-2 receptor (1,200 U/mL, normal range <474 U/mL), total IgG (2,472 mg/dL, <1,747 mg/dL), and IgG4 (2,040 mg/dL, <121 mg/dL) levels were elevated; however, other routine laboratory investigations, including complement levels, showed no remarkable abnormalities. Tests for serum angiotensin-converting enzyme, anti-neutrophil cytoplasmic, anti-SS-A/B, anti-double-stranded

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DNA, anti-nuclear, anti-ganglioside, anti-M-type phospholipase A2 receptor, and anti-NF 155 antibodies were all negative. M protein, paraneoplastic antibodies, vitamins B1 and B12, and copper were also negative. The urine test was negative for red blood cells (<1/high-power field), and the protein/creatinine ratio was 1.49 g/g Cre, indicating proteinuria. A cerebrospinal fluid analysis showed an increased protein level (79.4 mg/dL) with a normal glucose level and cell count; no malignant cells were observed on a cytological examination. Head and spinal magnetic resonance imaging (MRI) and whole-body computed tomography revealed no marked abnormalities.

Nerve conduction studies performed as described previously (4) showed prolonged distal motor latency and decreased motor nerve conduction velocity in the median, ulnar, and tibial nerves, consistent with demyelinating sensorimotor polyneuropathy (Table). Furthermore, sensory nerve action potential amplitudes in the median, ulnar, and sural nerves were markedly decreased or not elicited.

Under light microscopy, toluidine blue staining of the sural nerve biopsy specimen showed mild edema in the endoneurium (Figure A). The density of large- and small-diameter myelinated fibers was mildly decreased. Hematoxylin and Eosin staining showed cellular infiltration of mainly plasma cells and lymphocytes in the epineurium around the small vessel (Figure B). IgG4 immunostaining showed infiltration of IgG4-positive plasma cells in the epineurium. Scale bar indicates 50 μm.
noidal axon-glial detachment.

Based on the electrophysiological results, CIDP was diagnosed, and intravenous immunoglobulin treatment (IVIg, 400 mg/kg/day for 5 days) was initiated. His symptoms improved shortly after the first dose but were not responsive to the second course of IVIg. Therefore, methylprednisolone pulse (1 g/day for 3 days) and oral prednisolone were started, and the symptoms improved gradually. At that time, a serum examination revealed positive findings for anti-CNTN1 antibody (cell-based flow cytometry assay performed by H.O.) before the initiation of treatment. A subsequent examination revealed that the IgG subclass was IgG4-dominant, and antibody titers decreased from 3.3 in the pre-treatment serum to 0.1 (optical density values of serum dilution 1:500) in the post-treatment serum (enzyme-linked immunosorbent assay performed by Y.F.). His symptoms improved with treatment, and a decrease in serum IgG4 levels was observed. Urine protein was also no longer observed. He had been unable to walk when he was hospitalized, but he could walk with a single cane five months later, when a reexamination of nerve conduction showed electrophysiological improvement (Table).

Discussion

CIDP patients with disease-specific antibodies targeting paranodal proteins reportedly differ from typical CIDP patients with regard to immunopathological mechanisms, clinical features, and therapeutic responses. Thus, the latest edition of the European Academy of Neurology/Peripheral Nerve Society CIDP diagnostic guidelines (5) defined these as cases of autoimmune nodopathy. Patients with CNTN1 IgG4 antibodies have been described in a subgroup of CIDP patients with an elderly onset, sensory ataxia, and a poor response to IVIg (2, 6). CNTN1 is the myelin ligand of NF 155 at the paranode, where localization around the node of Ranvier is essential for saltatory conduction (6). Anti-CNTN1 antibodies affect the glial-axon interaction and functional organization of the node of Ranvier, thereby inducing paranodal dissection that might be responsible for the neurophysiological findings of slow velocities and conduction blocks. The present case had the characteristics of an anti-CNTN1 antibody-positive patient. Still, it was atypical in that the ultrastructural examination did not show the obvious paranodal axo-glial detachment that was previously described (7). In our case, the absence of axo-glial detachment may suggest that functional impairments resulting from the attachment of an anti-CNTN1 antibody precede morphological abnormalities development because the response to treatment was favorable. A recent report suggested that anti-CNTN1 autoantibodies influenced the function of dorsal root ganglion neurons by affecting the expression of contactin-1 and sodium currents (8), lending support to this view.

It was recently reported that anti-CNTN1 antibody-positive patients present with various complications, including membranous nephropathy (9, 10), malignant tumors (11), and diabetes mellitus (12). The patient was positive for urine protein but did not meet the criteria for nephrosis. Since a renal biopsy was not performed, a diagnosis of membranous nephropathy was not made. However, the patient’s proteinuria improved with steroid therapy, suggesting that renal involvement was related to the pathophysiology of this case.

In the present case, the serum IgG4 level was markedly elevated, and there was IgG4-positive plasma cells infiltration in the epineurium, which required differentiation from IgG4-related neuropathy. Peripheral neuropathy is associated with some IgG4-related diseases, and nerve biopsy findings show small vessel occlusion and fibrosis in the epineurium in such cases (13). However, these pathological findings were not observed in this case, and their relevance to this disease was unknown. Alternatively, a large amount of polyclonal IgG4 antibodies might have incidentally reacted with the CNTN1 antigen. Further studies are needed to clarify the significance of IgG4-positive plasma cell infiltration in anti-CNTN1 antibody-positive neuropathies.

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

References

1. Lehmann HC, Burke D, Kuwabara S. Chronic inflammatory demyelinating polyneuropathy: update on diagnosis, immunopathogenesis and treatment. J Neurol Neurosurg Psychiatry 90: 981-987, 2019.
2. Querol L, Nogales-Gadea G, Rojas-Garcia R, et al. Antibodies to contactin-1 in chronic inflammatory demyelinating polyneuropathy. Ann Neurol 73: 370-380, 2013.
3. Devaux JJ, Miura Y, Fukami Y, et al. Neurofascin-155 IgG4 in chronic inflammatory demyelinating polyneuropathy. Neurology 86: 800-807, 2016.
4. Koike H, Hirayama Y, Yamamoto M, et al. Age associated axonal features in HNPP with 17p11.2 deletion in Japan. J Neurol Neurosurg Psychiatry 76: 1109-1114, 2005.
5. Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force - second revision. Eur J Neurol 28: 3556-3583, 2021.
6. Miura Y, Devaux JJ, Fukami Y, et al. Contactin 1 IgG4 associates to chronic inflammatory demyelinating polyneuropathy with sensory ataxia. Brain 138: 1484-1491, 2015.
7. Koike H, Kadoya M, Kaida KI, et al. Paranodal dissection in chronic inflammatory demyelinating polyneuropathy with anti-neurofascin-155 and anti-contactin-1 antibodies. J Neurol Neurosurg Psychiatry 88: 465-473, 2017.
8. Grüner J, Stengel H, Werner C, et al. Anti-contactin-1 antibodies affect surface expression and sodium currents in dorsal root ganglia. Neurol Neuroimmunol Neuroinflamm 8: e1056, 2021.
9. Le Quintrec M, Teisseire M, Bec N, et al. Contactin-1 is a novel target antigen in membranous nephropathy associated with chronic inflammatory demyelinating polyneuropathy. Kidney Int 100: 1240-1249, 2021.
10. Cortese A, Lombardi R, Briani C, et al. Antibodies to neurofascin, contactin-1, and contactin-associated protein 1 in CIDP: clinical relevance of IgG isotype. Neurol Neuroimmunol Neuroinflamm 7: 1343.
11. Dubey D, Honorat JA, Shelly S, et al. Contactin-1 autoimmunity: serologic, neurologic, and pathologic correlates. Neurol Neuroimmunol Neuroinflamm 7: e771, 2020.

12. Appeltshauser L, Messinger J, Starz K, et al. Diabetes mellitus is a possible risk factor for nodo-paranodopathy with antiparanodal autoantibodies. Neurol Neuroimmunol Neuroinflamm 9: e1163, 2022.

13. Ohyama K, Koike H, Iijima M, et al. IgG4-related neuropathy: a case report. JAMA Neurol 70: 502-505, 2013.