IgG4-Related Peripheral Neuropathy with Unilateral Cervical Nerve Root and Brachial Plexus Swelling: A Case Report

Monami Tarisawa, Takahiro Kano, Daiki Tanaka, Masanao Yoshino, Hideki Houzen
Department of Neurology, Obihiro-Kosei General Hospital, Obihiro, Japan

Keywords
IgG4-related disease · IgG4-related neuropathy · $^{18}$F-fluorodeoxyglucose positron emission tomography · Biopsy

Abstract
A 64-year-old man presented with left upper limb weakness and dysesthesia for 4 months. Magnetic resonance imaging demonstrated swelling from the 6th–8th left cervical nerve roots to the left brachial plexus. The serum IgG4 level was elevated (762.7 mg/dL). $^{18}$F-FDG-PET showed high uptake in the mediastinal lymph nodes, and biopsy revealed infiltration of IgG4-positive plasma cells. We diagnosed IgG4-related neuropathy, and steroid therapy administration improved the symptoms. IgG4-related disease should be considered in the differential diagnosis of peripheral nerve swellings. If biopsy of the disordered nerves is difficult, lymph nodes or other organs should be considered.

Introduction
IgG4-related disease (IgG4-RD) is a newly designated disease concept that has been well known in Japan since the report on high serum IgG4 levels in autoimmune pancreatitis in 2001 [1]. Diagnostic criteria for IgG4-RD were proposed in 2011, and in February 2014, a research group of the Ministry of Health, Labor, and Welfare in Japan defined the disease. The disease affects systemic organs, such as the pancreas, hepatobiliary glands, salivary glands,
lacrical glands, retroperitoneal space, aorta, lungs, and kidneys [2]. Herein, we report a case of a patient with IgG4-related peripheral neuropathy with unilateral cervical radiculopathy. Although reports of peripheral neuropathy associated with IgG4-RD are limited, the disease may be overlooked and remain undiagnosed in some asymptomatic cases. We report the clinical and pathological features of IgG4-related peripheral neuropathy with a literature review.

Case Report

A 64-year-old man presented to our department with complaints of progressive weakness of the distal muscles in the left upper limb and a tingling sensation from the left 1st–3rd digits to the left forearm, which started 4 months before admission. He was suspected of having peripheral neuropathy and was admitted to our hospital (1st day after admission). He had a history of postoperative inguinal hernia, dyslipidemia, hypertension, and bronchial asthma. He had no family history of neuromuscular diseases. He had smoked 30–40 cigarettes daily for 25 years but did not consume alcohol.

On admission, his height and weight were 169 cm and 72 kg, respectively. His body temperature was 36.1°C; blood pressure, 150/82 mm Hg; pulse, 82 beats per minute; and oxygen saturation on ambient air, 96%. He was fully conscious and had no cranial nerve symptoms, including facial paralysis or paresthesia. The manual muscle testing grades (right/left) were as follows: triangular muscle, 5/5; musculus supraspinatus, 5/4; musculus infraspinatus, 5/4; musculus serratus anterior, 5/5; biceps brachii, 5/4+; triceps brachii, 5/4+; musculus extensor carpi radialis, 5/4; musculus flexor carpi radialis, 5/4; superficial flexor digitorum superficialis, 5/4; flexor digitorum superficialis, 5/4; total finger extensor muscle, 5/4; musculus opponens pollicis, 5/4; and musculus abductor pollicis brevis, 5/4. There was no muscle weakness in the neck or lower limbs. The patient’s grip strength was 45.9 kg/9.8 kg. The deep tendon reflex was mildly diminished in the left triceps. Dysesthesia and hypothermoalgesia were observed from the left 1st–3rd digits to the radial side of the forearm. There were no signs of ataxia or autonomic disturbance and no abnormalities in standing or walking. Laboratory tests showed no abnormalities in blood cells, liver or renal function, and CRP levels; however, the erythrocyte sedimentation rate was 53 mm/h, which was considered high. The vitamin B1 level was low at 23 ng/mL (reference range, 24–66 ng/mL), and the soluble interleukin-2 receptor level was mildly elevated at 805 U/mL (reference range, 122–496 U/mL). Immunoglobulin G (IgG) level was high at 2,205 mg/dL (reference range 870–1,700) as well as IgG4, 762.7 mg/dL (reference range 11–121), and IgE levels, 1,540 IU/mL (reference range 0–250); the complement titers, such as those of C4, C3, and CH50, were normal. The antinuclear antibody titer was 1:320, while those of anti-SS-A/SS-B antibody, MPO-ANCA, PR3-ANCA, and anti-ganglioside antibody were negative. On cerebrospinal fluid analysis, the initial pressure was 230 mm H2O; total protein level, 46 mg/dL (reference range 10–40); and glucose level, 64 mg/dL (reference range 50–75; simultaneous blood glucose, 97 mg/dL). There were 10 white cells per microliter (mononuclear cells were 10/μL), and soluble IL-2 receptor levels in the cerebrospinal fluid were lower than 50 U/mL. Cerebrospinal fluid cytology results were negative. Anti-neurofascin 155 (NF155) and anti-contactin-1 antibodies were negative in the serum and cerebrospinal fluid. Magnetic resonance imaging (MRI) showed extensive peripheral nerve swelling, from the left 6th–8th left cervical nerve root to the brachial plexus, all of which had high-intensity lesions on gadolinium-enhanced imaging (shown in Fig. 1). No abnormalities were observed in the lumbar plexus. Computed tomography showed mild swelling of the hilar and mediastinal lymph nodes bilaterally. Nerve conduction studies (NCS) revealed no abnormalities in distal latency, motor nerve conduction velocity, and amplitude of complex muscle action potential and sensory nerve action potential.
Sensory NCS of the lateral and medial antebrachial cutaneous nerves were not performed. ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG-PET) showed high uptake in the left brachial plexus, right parapharyngeal (SUVmax 10.5), and bilateral hilar lymph nodes (SUVmax 5.16) (shown in Fig. 2).

Initially, we suspected focal chronic inflammatory demyelinating polyneuropathy (CIDP), vasculitis, or malignant lymphoma; however, because of the lack of systemic symptoms, such
as fever, night sweats, and weight loss, and negative laboratory findings of other organ damage and monoclonal immunoglobulins, none of these diagnoses were subsequently considered. Neuralgic amyotrophy was also not considered because of the lack of preceding pain. Thiamine was supplemented from the 13th day for vitamin B₁ deficiency, but the symptoms did not improve. Because of the high levels of serum IgG4 and IgE, both of which might have been induced by Th2 cytokines, IgG4-RDs were finally considered; thus, needle biopsy was performed on the mediastinal lymph nodes in which ¹⁸F-FDG-PET showed high uptake; however, no histologically significant findings were observed. On the 42nd day, thoracoscopic mediastinal lymph node biopsy was performed. Histopathological examination of a subcarinal lymph node revealed infiltration of lymphocytes and plasma cells into the paracortical area, and immunostaining revealed CD138-positive plasma cell infiltration. The IgG4/IgG ratio was 0.8, and the number of IgG4-positive cells was 200 cells/HPF (shown in Fig. 3). IgG4-RD associated with peripheral neuropathy (IgG4-related peripheral neuropathy) was diagnosed based on the comprehensive diagnostic criteria of 2020 [3]. Methylprednisolone pulse therapy was administered on the 43rd day, which was switched to oral prednisolone on the 46th day. By the 50th day, the muscle weakness and dysesthesia had gradually improved, the manual muscle testing grade was 5 in most of the proximal and distal muscles in the upper left limbs, and the left grip strength had improved to 22.5 kg. The serum IgG4 level had decreased to 446.8 mg/dL by the 58th day. The enlarged nerve roots and brachial plexus continued to shrink, and the contrast effect was weakened on MRI. The patient was discharged on the 67th day when oral prednisolone was reduced to 30 mg/day. The symptoms did not recur, peripheral nerves swelling improved on imaging, and serum IgG4 level decreased to 111.7 mg/dL a month after discharge.

Fig. 3. Histologic findings of the mediastinal lymph node. Abundant CD138-positive plasma cell infiltration is observed. The ratio of IgG4-positive plasma cells/IgG-positive cells is approximately 80%. a Hematoxylin and eosin (H&E) staining; original magnification, ×100. b CD138 immunohistochemical staining; original magnification, ×100. c IgG immunostaining; original magnification, ×100. d IgG4 immunostaining; original magnification, ×100.
Discussion

IgG4-RD is characterized by high serum IgG4 levels, histologically polyclonal IgG4 plasma cell infiltration, storiform fibrosis, obliterative phlebitis, and various clinical features depending on the affected organ. The diagnostic criteria for IgG4-RD in 2020 are shown in Table 1 [3]. In addition, it is important to exclude malignant tumors of each organ (solid cancer, malignant lymphoma, etc.) and similar inflammatory diseases (Sjögren’s syndrome, primary/secondary sclerosing cholangitis, Castleman disease, secondary retroperitoneal fibrosis, granulomatosis with polyangiitis, sarcoidosis, and eosinophilic granulomatosis with polyangiitis).

It has been reported that IgG4-RD, such as pachymeningitis, orbital disease, peripheral nerve diseases, as well as brain parenchyma, pituitary gland, and stalk disease, involves the central and peripheral nervous systems [4]. Nerve biopsy performed in case of peripheral nerve disease generally selects the sural nerve, which has few anatomical variations and does not contain motor nerves. However, in some cases of IgG4-RD, lesions are only identified in a single organ and pathologically significant findings may be lacking in the absence of neurological symptoms in the sural nerve region; hence, confirming the diagnosis is difficult.

IgG4-related peripheral neuropathy was first reported by Ohyama et al. [5]. The patient's clinical symptoms showed multiple mononeuropathy patterns, which may be due to the infiltration of inflammatory cells and fibrosis of the epineurium, thereby obstructing the vessels and causing ischemia of the peripheral nerves, resulting in axonal neuropathy. Moreover, in 2015, Ohyama et al. [6] retrospectively examined 149 cases of patients with inflammatory peripheral neuropathy who underwent sural nerve biopsy; serum IgG4 level >135 mg/dL was observed in 35 cases, and 29 cases had IgG4-positive cell infiltration. These cases were classified as microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, Sjögren’s syndrome, and rheumatoid arthritis. These findings suggest that IgG4-positive cell infiltration is detected even in diseases that need to be differentiated from IgG4-RD. However, even after excluding these related diseases, five cases that were not diagnosed before and after the biopsy still met the criteria for IgG4-RD. IgG4-related peripheral neuropathy may have been overlooked in inflammatory peripheral neuropathy, whose pathology was previously unknown.

Similar to our case, the incidence of peripheral nerve swelling affecting the suborbital, supraorbital, infraorbital, optic, greater auricular nerves, and spinal nerve root as a feature

Table 1. The 2020 revised comprehensive diagnostic criteria for IgG4-RD[3]

| Item | Clinical and radiological features |
|------|----------------------------------|
| 1    | One or more organs show diffuse or localized swelling or a mass or nodule characteristic of IgG4-RD. In single organ involvement, lymph node swelling is omitted. |
| 2    | Serum IgG4 levels greater than 135 mg/dL. |
| 3    | Positivity for two of the following three criteria: Dense lymphocyte and plasma cell infiltration with fibrosis. Ratio of IgG4-positive plasma cells/IgG-positive cells greater than 40% and the number of IgG4-positive plasma cells greater than 10 per high-powered field. Typical tissue fibrosis, particularly storiform fibrosis, or obliterative phlebitis. |

Diagnosis:
- **Definite**: (1) + (2) + (3)
- **Probable**: (1) + (3)
- **Possible**: (1) + (2)

...
of IgG4-related peripheral neuropathy was first reported by Inoue et al. [7]. Of the 109 patients with IgG4-RD, 7 patients had peripheral nerve swelling, and 5 patients had multiple nerve findings. Most cases include peripheral neuropathy in the orbital region (four intraorbital nerves and three optic nerves) as well as spinal radiculopathy (two cases). The swollen nerve reached a diameter of 8–30 mm. IgG4-positive plasma cell infiltration is pathologically observed in the perineurium, but since inflammation does not extend to the endoneurium, the axon is not disordered. Therefore, vision loss or diplopia is likely to occur when the nerves in the orbital region are damaged, but in case that only the spinal nerve roots are damaged, most cases are asymptomatic. In addition, all patients also had IgG4-RD lesions in other organs, such as the extraocular muscles, salivary glands, and lymph nodes; thus, performing biopsy of these organs should be considered.

There are still many unclear points regarding the role of IgG4 in IgG4-RD. Activated B cells and CD4-positive cytotoxic T cells are considered to be the main causes of inflammation and fibrosis, but IgG4 itself does not induce inflammation due to its characteristics [2]. Therefore, no conclusion has been drawn on whether IgG4 is pathogenic or is produced reactively as a result of an immune response. In contrast, unilateral peripheral nerve swelling also caused by IgG4-subclass antibody-positive autoimmune nodopathies targeting contactin-1, NF155, and Caspr1 expressed in the nodes of Ranvier and its neighboring paranodes [8, 9] need to be differentiated from IgG4-related peripheral neuropathy. IgG4-subclass antibody-positive autoimmune nodopathies have recently been established as a disease concept independent of CIDP because their clinical presentations differ from those of typical CIDP [8]. In the case of anti-NF155 antibody-positive autoimmune nodopathy, no inflammatory cell infiltration was observed. Furthermore, histopathological examination revealed detachment of the terminal Schwann cell loops from the axons at the paranodes, resulting in the inhibition of the interaction between NF155 and contactin-1/Caspr1, thereby causing demyelination [8]. Therefore, IgG4-related peripheral neuropathy and IgG4-subclass antibody-positive autoimmune nodopathies have different pathophysiologies. NCS is useful in differentiating between IgG4-related peripheral neuropathy and autoimmune nodopathy; however, demyelination or axonal damage may not be detected for damage limited to the plexus; consequently, 18F-FDG-PET and histopathological findings may be useful for differentiation [10].

Corticosteroid, which is the first-line and standard-of-care treatment, is effective in treating IgG4-RD [2]. However, steroid-resistant cases have been reported because of irreversible nerve damage [11]. Combination with other immunosuppressive agents, such as azathioprine, mycophenolate mofetil, and rituximab, is also a treatment option, but there is little evidence of therapeutic effects in either case [4]. IgG4 is not considered to be pathogenic to the complement and Fc regions targeted by IVIg [12, 13]; therefore, IVIg has little effect on IgG4-RD.

In the current case, symptomatic neuropathy localized in left upper limb was found, and it was thought that IgG4 infiltration extended not only to the perineurium but also to the endoneurium. Considering previous reports that most paravertebral cases are asymptomatic [7], our case is relatively rare. In addition, the lesion was localized from the left cervical nerve root to the left brachial plexus on imaging, and there was no neuropathy in the sural nerve; therefore, biopsy of the sural nerve was not performed. The pathological findings on lymph node biopsy and steroid reactivity are helpful in diagnosing IgG4-RD. In cases where biopsy is difficult, whole-body imaging, especially 18F-FDG-PET examination, is useful for the diagnosis of other organ lesions that have no obvious findings on computed tomography examination.

IgG4-RD should be considered in patients with multiple radiculopathy or peripheral nerve swelling, even in the absence of lesions in other organs. If nerve biopsy is difficult, 18F-FDG-PET is useful in searching for multi-organ lesions to perform histological examination for diagnosis, and corticosteroid treatment should be started as early as possible.
Acknowledgments

The authors thank Dr. Hideki Ogata and Dr. Noriko Isobe (Department of Neurology, Graduate School of Medicine, Kyushu University, Fukuoka, Japan) for measuring the anti-NF155 antibody and anti-contactin antibody levels.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patient described in this paper gave written informed consent to publication of the case, including publication of images. Ethical approval is not required for this study in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflict of interest to report.

Funding Sources

No author has received any funding for the conduct, authorship, or publication of this study.

Author Contributions

Monami Tarisawa contributed to medical treatment, data acquisition, drafting, and writing. Takahiro Kano, Daiki Tanaka, and Masanao Yoshino contributed to medical treatment and data acquisition and critically reviewed the manuscript. Hideki Houzen contributed to supervision and approved the final draft.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 2001;344(10):732–8.
2. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet. 2015;385(9976):1460–71.
3. Umehara H, Okazaki K, Kawa S, Takahashi H, Goto H, Matsui S, et al. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. Mod Rheumatol. 2021;31(3):529–33.
4. AbdelRazek MA, Venna N, Stone JH. IgG4-related disease of the central and peripheral nervous systems. Lancet Neurol. 2018;17(2):183–92.
5. Ohyama K, Koike H, Iijima M, Hashimoto R, Tomita M, Kawagashira Y, et al. IgG4-related neuropathy: a case report. JAMA Neurol. 2013;70(4):502–5.
6. Ohyama K, Koike H, Takahashi M, Kawagashira Y, Iijima M, Watanabe H, et al. Immunoglobulin G4-related pathologic features in inflammatory neuropathies. Neurology. 2015;85(16):1400–7.
7. Inoue D, Zen Y, Sato Y, Abo H, Demachi H, Uchiyama A, et al. IgG4-related perineural disease. Int J Rheumatol. 2012;2012:401890.
8 Kira JI, Yamasaki R, Ogata H. Anti-neurofascin autoantibody and demyelination. Neurochem Int. 2019; 130: 104360.
9 Vallat JM, Magy L, Corcia P, Boulesteix JM, Uncini A, Mathis S. Ultrastructural lesions of nodo-paranodopathies in peripheral neuropathies. J Neuropathol Exp Neurol. 2020; 79(3): 247–55.
10 Zhang J, Chen H, Ma Y, Xiao Y, Niu N, Lin W, et al. Characterizing IgG4-related disease with 18F-FDG PET/CT: a prospective cohort study. Eur J Nucl Med Mol Imaging. 2014; 41(8): 1624–34.
11 Suzuki Y, Shiraishi M, Yamada K, Doi M, Kato M, Hasegawa Y. A case of refractory IgG4-related peripheral neuropathy with severe axonal damage. Rinsho Shinkeigaku. 2016; 56(5): 323–7.
12 Querol L, Nogales-Gadea G, Rojas-Garcia R, Díaz-Manera J, Pardo J, Ortega-Moreno A, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. Neurology. 2014; 82(10): 879–86.
13 Tackenberg B, Nimmerjahn F, Lünemann JD. Mechanisms of IVIg efficacy in chronic inflammatory demyelinating polyneuropathy. J Clin Immunol. 2010; 30(Suppl 1): S65–69.