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【 CASE REPORT 】

Pyrexia-associated Relapse in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Abstract:
Chronic inflammatory demyelinating polyradiculoneuropathy is a relapsing-remitting or chronic progressive demyelinating polyradiculoneuropathy. We report the case of a patient with chronic inflammatory demyelinating polyradiculoneuropathy who experienced relapses on four occasions after experiencing pyrexia and flu-like symptoms. Our patient showed characteristic features, such as relapse after pyrexia and flu-like symptoms, remission after pyretolysis without treatment, and the absence of remarkable improvement in a nerve conduction study in the remission phase. The serum level of tumor necrosis factor-α was elevated in the relapse phase and reduced in the remission phase; thus, the induction of cytokine release by viral infection might have caused the relapses.

Key words: chronic inflammatory demyelinating polyradiculoneuropathy, demyelinating diseases, nerve conduction study, blood-nerve barrier

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Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a relapsing-remitting or chronic progressive demyelinating polyradiculoneuropathy (1), which includes heterogeneous subtypes with various clinical and neurophysiological characteristics. We describe the case of a patient with CIDP, who experienced relapses on four occasions after experiencing pyrexia and flu-like symptoms, and discuss the possible pathophysiology of pyrexia-associated relapses in CIDP.

Case Report

The patient was a right-handed 56-year-old woman without a family history of neuropathy, who could independently perform activities of daily living (ADL). In 2010, she was admitted to another hospital due to the acute onset of left abducens paralysis, limb muscle weakness, sensory disturbance, and paresthesia, which was preceded by the manifestation of pyrexia and flu-like symptoms two days previously. A nerve conduction study (NCS) showed demyelinating polyneuropathy with conduction block. On admission, her body temperature was 38.1°C, and she was unable to walk. She was treated with intravenous immunoglobulin based on a diagnosis of Guillain-Barré syndrome (GBS). Her symptoms gradually improved after pyretolysis, and two weeks later, she had almost fully recovered and was discharged. The patient was negative for anti-GM1, anti-GD1a, anti-GD1b and anti-GQ1b IgG antibodies, but positive for anti-GalNAc-GD1a IgG antibodies.

In 2012 and 2013, she experienced two relapses, which were preceded by pyrexia (38.6°C and 39.2°C, respectively) and flu-like symptoms, which manifested one day and three days previously, respectively. Her symptoms gradually improved after pyretolysis without treatment; however, paresthesia of the toes remained after the third relapse.

In 2016 she developed gait disturbance and diplopia (Day 1), which was preceded by pyrexia and flu-like symptoms, which manifested one day previously. By Day 2, she was unable to walk and by Day 3, she became unable to stand upright. She visited the emergency department of our medical center on Day 4. On arrival, her body temperature was 38.2°C. A neurological examination showed left abducens paralysis, decreased position, vibratory, pinprick and touch

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Table 1. Nerve Conduction Study in the Fourth Relapse Phase and Remission Phase.

MCS						
Nerve	Side	Phase	Distal Lat, ms	Amp, mV	CV, m/S	Fw, Minimal Lat, ms
Median	R	Relapse	3.5	7.4	**20**	**51.5**
		Remission	3.2	10.0	**22**	**50.9**
	L	Relapse	3.0	7.3	**27**	**46.2**
		Remission	3.8	8.7	**38**	**38.4**
Ulnar	R	Relapse	2.5	**3.3**	**23**	**47.1**
		Remission	2.6	**4.6**	**22**	**48.3**
	L	Relapse	3.0	6.0	60	**42.2**
		Remission	**3.2**	8.1	55	**40.3**
Tibial	R	Relapse	4.0	15.3	**39**	**88.7**
		Remission	4.6	16.7	**36**	**77.6**
	L	Relapse	4.8	16.6	41	**87.4**
		Remission	4.7	15.3	42	**80.8**

SCS					
Nerve	Side	Phase	Distal Lat, ms	Amp, μV	CV, m/S
Median	R	Relapse	2.4	17.4	61
		Remission	2.2	**6.5**	63
	L	Relapse	2.0	11.0	58
		Remission	2.9	**6.5**	52
Ulnar	R	Relapse	2.3	**6.0**	56
		Remission	2.0	**3.4**	54
	L	Relapse	2.1	11.2	48
		Remission	2.3	8.2	47

Abnormal data by the standard of our medical center is shown in boldface. Height of the patient was 157 cm. R: right, L: left, MCS: motor nerve conduction study, SCS: sensory nerve conduction study, Lat: latency, Amp: amplitude, CV: conduction velocity, Fw: F wave

senses of the limbs, absent deep tendon reflexes, and asymmetric distal-dominant muscle weakness and paresthesia of the limbs. She was unable to stand unsupported due to muscle weakness and sensory ataxia. Laboratory studies revealed a white blood cell count of 5,300/mm^3, and increased CRP (7.63 mg/dL). Her vitamin B_1, B_6, B_{12}, and folic acid levels were normal. She was negative for antinuclear antibodies, anti SS-A and SS-B antibodies, anti-MAG antibodies, M protein, anti-GM1 antibodies, and anti-GQ1b IgG. Her anti-GalNAc-GD1a IgG antibody titer could not be checked because she refused to undergo the test. Her serum levels of tumor necrosis factor-α (TNF-α) were elevated (5.73 pg/mL). Lumbar puncture showed 2 white blood cells/mm^3 (including 100% mononuclear cells) and 18 mg/dL of protein. The patient was negative for the oligoclonal band and myelin basic protein, and her IgG-index value was 0.5. The NCS showed demyelinating polyneuropathy with conduction block in the median, ulnar, and tibial nerves. The asymmetric clinical symptoms and multifocal demyelination in the NCS suggested a variant of CIDP, multifocal acquired demyelinating sensory and motor neuropathy. After pyretolysis without antipyretics on Day 5, the patient became able to stand up and walk with assistance due to the improvement of her muscle weakness and sensory ataxia; her left abducens paralysis began to improve on Day 6, without treatment. She became able to walk without assistance on Day 7. Her symptoms gradually improved, and on Day 14, she discharged on foot with the disappearance of diplopia and left abducens paralysis, and the improvement of sensory ataxia; however, the paresthesia of the feet remained. At seven months after admission, an NCS demonstrated no remarkable improvement in the fourth remission phase in comparison to that in the fourth relapse phase, with the exception of a tendency toward a shorter minimal F wave latency in the fourth remission phase (Table 1). The serum level of TNF-α in the fourth remission phase was decreased (Table 2).

Discussion

Our patient showed characteristic features, such as relapses after pyrexia and flu-like symptoms, remissions after pyretolysis without treatment, and the absence of remarkable improvement in the NCS results in the remission phase.

The differential diagnosis of CIDP includes various diseases, such as neurolymphomatosis, neurosarcoidosis, and hereditary neuropathy to pressure palsies (HNPP). In our patient, the long and benign clinical course was not compatible with neurolymphomatosis. The absence of pulmonary, ocu-

Table 2. Serum Cytokines in the Fourth Relapse Phase and Remission Phase.

Serum cytokine	Phase	Serum level
IL-1β (pg/mL)	Relapse	0.799
(Normal value, <0.928 pg/mL)	Remission	<0.125
IL-2 (pg/mL)	Relapse	<15.6
(Normal value, <15.6 pg/mL)	Remission	<15.6
TNF-α (pg/mL)	Relapse	5.73
(Normal value, <1.79 pg/mL)	Remission	2.22

IL-1β: interleukin-1β, IL-2: interleukin-2, TNF-α: tumor necrosis factor-α

lar, and cutaneous symptoms in 7 years and the acute deterioration after pyrexia were also incompatible with neurosarcoidosis. Abducens paralysis and deterioration in association with pyrexia have never been reported in HNPP. Furthermore, the absence of a family history of neuropathy, the absence of a past history of compression neuropathy, and the presence of conduction block at sites other than the compression sites on the NCS were incompatible with HNPP; however, a genetic examination was not performed in accordance with the patient's wishes.

Although CIDP is defined as having a chronic onset of at least 2 months (1), CIDP patients sometimes show a rapid and progressive course (acute-onset CIDP), which resembles GBS (2, 3). In previous studies, the relapse of GBS relapse was reported to be rare (4), and some GBS patients are later diagnosed with CIDP after relapse and remission (5). Our patient was initially diagnosed with GBS, but she experienced relapse and remission on four occasions, and her paresthesia gradually deteriorated over six years. Thus, we diagnosed her condition as CIDP, rather than recurrent GBS.

The present patient was positive for anti-GalNAc-GD1a IgG antibodies. It is hypothesized that GalNAc-GD1a was present in the ventral root, particularly in the nodes of Ranvier and the paranodal region (6). Anti-GalNAc-GD1a IgG antibodies are closely associated with the pure motor variant of GBS, which is characterized by distal-dominant limb weakness and infrequent cranial nerve involvement (7); however, they are occasionally seen in other diseases, such as neurosarcoidosis and CIDP (8, 9). The correlation between the clinical and neurophysiological characteristics in CIDP and the anti-GalNAc-GD1a IgG antibody remains unclear.

To the best of our knowledge, only one case of pyrexia-associated relapse in CIDP has been reported, by Mazzucco et al. (10). There are some similarities between the two patients. First, they were independent in the remission phase of ADL; however, the symptoms deteriorated acutely after pyrexia and flu-like symptoms, and gradually improved after pyretolysis, without treatment. Second, the symptoms were stereotypical in every relapse. Third, the NCS showed demyelinating polyneuropathy with conduction block, but there was no remarkable improvement in the NCS findings in the remission phase. Finally, with the exception of anti-GalNAc-GD1a IgG antibodies, there was no evidence of other systemic, infectious, immunological, and metabolic disease that could have caused demyelinating neuropathy in our patient. On the other hand, there were several different points between our patient and the patient reported by Mazzucco et al. First, our patient showed left abducens paralysis, while their patient showed no evidence of cranial nerve palsy. Second, although the cerebrospinal fluid protein level was elevated in their patient, it was normal in our patient. Third, the NCS in their case demonstrated sensory-dominant demyelination, while the NCS in our case revealed the motor-dominant demyelination.

The pathophysiology of pyrexia-associated relapse in CIDP is unknown. Mazzucco et al. hypothesized that pyrexia-associated relapses in CIDP could occur due to the elevation of the core body temperature, which is similar to the cause of Uhthoff's phenomenon in multiple sclerosis (10). An increased temperature causes reversible conduction block in demyelinated fibers (11), but the symptoms in our patient did not disappear soon after pyretolysis; rather, they gradually improved within two weeks. Thus, we suggest that such persistent symptoms after pyretolysis could not be explained by Uhthoff's phenomenon, which usually lasts less than 24 hours (12).

Another possible reason for pyrexia-associated relapse in CIDP is nerve conduction abnormalities due to the induction of cytokine release by viral infection. Viral infection induces the release of cytokines, such as interleukin(IL)-1β, IL-2, and TNF-α (13). The injection of TNF-α into the peripheral nerves was shown to cause their inflammation and demyelination (14), and the association between CIDP and serum cytokines, including IL-1β, IL-2, and TNF-α, has been reported (15, 16). Furthermore, the serum TNF-α levels are correlated with the clinical severity of CIDP (17). In our patient, the serum level of TNF-α was elevated in the relapse phase and was decreased in the remission phase, which might suggest a correlation between cytokines and pyrexia-associated relapses in CIDP; however, we could not obtain pathological evidence to support this hypothesis because our patient refused to undergo nerve biopsy. The absence of a remarkable improvement in the NCS findings in the remission phase might indicate the proximal lesions in the peripheral nerves, as suggested in the previous report (10), and it is likely that cytokines affect the proximal lesions in the peripheral nerves, where the blood-nerve barrier is destroyed by chronic demyelination.

Conclusions

To our knowledge, this is the second reported case of pyrexia-associated relapse in CIDP. We suggest that persistent symptoms after pyretolysis were not simply explained by Uhthoff's phenomenon, and that the induction of cytokine release by viral infection might cause pyrexia-associated relapse in CIDP. Pyrexia-associated relapse is quite rare in patients with CIDP; thus, more detailed clinical analyses and the accumulation of cases will be necessary to

elucidate its pathophysiology.

Informed consent was obtained from all of the individual participants included in the study.

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

References

1. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. J Peripher Nerv Syst **10**: 220-228, 2005.
2. McCombe PA, Pollard JD, McLeod JG. Chronic inflammatory demyelinating polyradiculoneuropathy. A clinical and electrophysiological study of 92 cases. Brain **110**: 1617-1630, 1987.
3. Trojaborg W. Acute and chronic neuropathies: new aspects of Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy, an overview and an update. Electroencephalogr Clin Neurophysiol **107**: 303-316, 1998.
4. Das A, Kalita J, Misra UK. Recurrent Guillain-Barré syndrome. Electromyogr Clin Neurophysiol **44**: 95-102, 2004.
5. Odaka M, Yuki N, Hirata K. Patients with chronic inflammatory demyelinating polyneuropathy initially diagnosed as Guillain-Barré syndrome. J Neurol **250**: 913-916, 2003.
6. Kaida K, Kusunoki S, Kamakura K, Motoyoshi K, Kanazawa I. GalNAc-GD1a in human peripheral nerve: target sites of anti-ganglioside antibody. Neurology **4**: 465-470, 2003.
7. Kaida K, Kusunoki S, Kamakura K, et al. Guillain-Barré syndrome with antibody to a ganglioside, N-acetylgalactosaminyl GD 1a. Brain **123**: 116-124, 2000.
8. Chatani H, Tanaka M, Nagata T, Araki T, Kusunoki S. Guillain-Barré syndrome-like-onset neurosarcoidosis positive for immunoglobulin G anti-N-acetylgalactosaminyl-GD1a antibody. J Clin Neurosci **21**: 170-172, 2014.
9. Tatsumoto M, Odaka M, Koga M, Hirata K, Yuki N. Clinical features of neuropathies in a group of patients associated with anti-GalNAc-GD1a antibody. Rinsho Shinkeigaku (Clin Neurol) **44**: 508-512, 2004 (in Japanese, Abstract in English).
10. Mazzucco S, Ferrari S, Mezzina C, Tomelleri G, Bertolasi L, Rizzuto N. Hyperpyrexia-triggered relapses in an unusual case of ataxic chronic inflammatory demyelinating polyradiculoneuropathy. Neurol Sci **27**: 176-179, 2006.
11. Rasminsky M. The effects of temperature on conduction in demyelinated single nerve fibers. Arch Neurol **28**: 287-292, 1973.
12. Frohman TC, Davis SL, Beh S, Greenberg BM, Remington G, Frohman EM. Uhthoff's phenomena in MS-clinical features and pathophysiology. Nat Rev Neurol **9**: 535-540, 2013.
13. Mogensen TH, Paludan SR. Molecular pathways in virus-induced cytokine production. Microbiol Mol Biol Rev **65**: 131-150, 2001.
14. Redford EJ, Hall SM, Smith KJ. Vascular changes and demyelination induced by the intraneural injection of tumour necrosis factor. Brain **118**: 869-878, 1995.
15. Beppu M, Sawai S, Misawa S, et al. Serum cytokine and chemokine profiles in patients with chronic inflammatory demyelinating polyneuropathy. J Neuroimmunol **279**: 7-10, 2015.
16. Hartung HP, Reiners K, Schmidt B, Stoll G, Toyka KV. Serum interleukin-2 concentrations in Guillain-Barré syndrome and chronic idiopathic demyelinating polyradiculoneuropathy: comparison with other neurological diseases of presumed immunopathogenesis. Ann Neurol **30**: 48-53, 1991.
17. Misawa S, Kuwabara S, Mori M, Kawaguchi N, Yoshiyama Y, Hattori T. Serum levels of tumor necrosis factor-α in chronic inflammatory demyelinating polyneuropathy. Neurology **56**: 666-669, 2001.