

Single Case – General Neurology

Recurrent Guillain-Barré and Fisher Syndromes in Two Patients Who Were Subsequently Diagnosed with Aplastic Anemia

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Keywords

Guillain-Barré syndrome · Fisher syndrome · Recurrence · Aplastic anemia · HLA

Abstract

Guillain-Barré (GBS) and Fisher (FS) syndromes rarely recur and the characteristics of recurrence have not been fully elucidated. We describe the cases of 2 patients with GBS or FS that recurred more than twice and who were subsequently diagnosed with aplastic anemia. Case 1 was a 66-year-old man who was diagnosed with aplastic anemia 10 months before admission with limb ataxia and a sensory disturbance of the distal limbs that developed 3 days after an upper respiratory tract infection. He had a history of double vision with ataxia at the ages of 38 and 56 years. Case 2 was a 66-year-old woman who had been treated for aplastic anemia 1 year previously. She had a history of upper limb weakness after upper respiratory tract infections at the ages of 39 and 60 years. Tendon reflexes were absent in both patients at the time of onset and they were respectively diagnosed with FS and GBS and treated with intravenous

immunoglobulin. No neurological deficits persisted. Blood findings showed that both were positive for IgG type ganglioside antibodies and HLA-DR15. The positive HLA-DR15 might have been associated with the recurrent GBS or FS and the development of aplastic anemia.

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Introduction

Guillain-Barré syndrome (GBS) is a peripheral nerve disorder with acute weakness of the distal limbs and absent tendon reflexes [1]. Fisher syndrome (FS) is a subtype of GBS characterized by diplopia, ataxia, and the loss of deep-tendon reflexes [2]. The clinical course is generally monophasic, and the recurrence of both GBS and FS is rare. Although human leukocyte antigen (HLA) might be associated with recurrent GBS or FS, the characteristics of patients with such recurrence have not been fully elucidated [3]. We describe the cases of 2 patients with recurrent GBS and FS who were subsequently diagnosed as aplastic anemia.

Case Reports

Case 1

A 66-year-old man with aplastic anemia was admitted with a gait disturbance due to ataxia and a sensory disturbance of the distal limbs 3 days after an upper respiratory tract infection. He had a history of diplopia and ataxia after similar infections at the ages of 38 and 56 years, respectively, and was diagnosed with FS at the time of the second infection. He had been diagnosed with aplastic anemia accompanied by paroxysmal nocturnal hemoglobinuria (AA-PNH) by a bone-marrow biopsy 10 months before admission. Immunosuppressive therapy with anti-thymoglobulin and cyclosporine was performed for aplastic anemia, but the therapeutic effect was insufficient. The aplastic anemia was in remission under treatment with eltrombopag.

A neurological examination upon admission revealed limb ataxia, a sensory disturbance of the distal limbs, absent deep-tendon reflexes and decreased grip forces of 25 and 23 kg in the right and left hands, respectively. A complete blood count, biochemical and coagulation findings were normal. Cell counts were normal (7/3) and protein in cerebrospinal fluid samples was elevated (44 mg/dL). Nerve conduction findings were unremarkable in the right medial, ulnar, and tibial motor nerves. We diagnosed recurrent FS and treated him with intravenous immunoglobulin (0.5 g/kg). His neurological symptoms gradually improved, and he was able to walk independently 7 days after admission and was discharged 11 days from admission. His blood examination revealed positive IgG-type anti-ganglioside (GQ1b) antibody and HLA-DR15, negative IgM type GQ1b antibody.

Case 2

A 66-year-old woman had been diagnosed with aplastic anemia from a PNH clone 1 year before and treated with cyclosporin, and was currently in remission. She had a history of distal limb weakness with loss of deep-tendon reflexes at 7 days after upper respiratory tract infections at the ages of 39 and 60 years. A nerve conduction study during the second infection showed low amplitude; however, decreasing conduction speed or conduction block which suggested chronic inflammatory demyelinating polyneuropathy were not found in the right median motor nerve (NCV, 51.3 m/s; wrist, 4.150 mV; elbow, 1.570 mV). She was also positive

for IgG type GM-1 and GQ1b antibodies. She was diagnosed with recurrent GBS and treated with intravenous immunoglobulin (0.5 g/kg). Her neurological deficits disappeared, but she remained positive for HLA-DR15.

Discussion

These patients had a history of at least two recurrences of GBS or FS and were subsequently diagnosed with aplastic anemia. The reported rates of GBS occurrence in Japan are 0.62–2.66 per 100,000 and that of FS was almost one-third of GBS [4], and those of recurrence are 2–5 and 14%, respectively [2, 5]. Thus, GBS and FS are known to recur, but the frequency was admittedly rare.

The characteristics of recurrence have not been fully elucidated. Genetic factors might be involved in the development of GBS or FS. A relationship between HLA-DR2 and GBS has been suspected, but this remains debatable [6, 7]. On the contrary, Chida et al. [3] found that HLA-DR2 positivity might be associated with the occurrence of FS. The patients in their study were positive for HLA-DR15 (a subtype of HLA-DR2); thus HLA-DR15 might be involved in recurrent GBS or FS [8]. One notion is that GBS develops when peripheral nerves are damaged by cellular immunity. Because HLA-DR15 tends to induce Th0 cell differentiation into Th1 or Th17 cells that are associated with cellular immunity, patients who are HLA-DR15 positive might be more susceptible to developing GBS or FS [9–12]. However, as there are no studies which examined the correlation with HLA-DR15 and GBS or FS, further examination will be needed in the future.

Our patients were treated with cyclophosphamide or cyclosporin for AA-PNH. The mechanism of aplastic anemia is not fully understood: AA-PNH might be caused via a mechanism in which killer T cells attack blood cells under a PNH clone with but not without a GPI-anchored protein [13, 14]. Aplastic anemia is caused by autoimmune attack to hematopoietic stem cells, resulting in decrease in the number of stem cells. PNH clones derived from stem cells deficient in GPI-anchored proteins are present only below normal measurement sensitivity. However, in cases of aplastic anemia, since PNH clones remain resistant to attack by self-reactive lymphocytes, relatively expanded compared to normal stem cells, PNH clones are believed to be detectable. Because positive HLA-DR15 tends to suppress the activity of regulatory T cell that control the activity of killer T cells, hyperactive killer T cells might contribute to the onset of aplastic anemia [15, 16]. Kaya et al. [17] described a patient with aplastic anemia who developed GBS because T cell-controlled B-cell activation had been suppressed by the administration of anti-lymphocytes. In the case, treatment by intravenous immunoglobulin was effective for both GBS and aplastic anemia. Intravenous immunoglobulin has the effect of increasing regulatory T cell and suppression of tumor necrosis factor- α and interferon- γ [18]. This supported T cell was associated with both GBS and aplastic anemia. In addition, anchor protein might be associated with both aplastic anemia and GBS, as gangliosides that are targets in GBS are glycosphingolipids linked to an anchor protein [19].

We described 2 patients with recurrence of GBS and FS who were subsequently diagnosed with aplastic anemia. The recurrence of these pathologies and their association with HLA-DR15 require further investigation.

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Statement of Ethics

The study protocol was approved by the ethical review committee of Kyushu Medical Center. Informed consent was obtained from the patients to publish these cases in accordance with the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Saori Tomohara, Risa Harano, Shinichi Wada, Ikkei Ohashi, Fumitaka Yoshino, and Daiki Mito reviewed the clinical data, made literature search, and drafted the manuscript. Masanori Kadowaki, Ken Takase, Takahiro Kuwashiro, Hitonori Takaba, Masahiro Yasaka, and Yasushi Okada revised the manuscript.

References

- 1 Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. *Ann Neurol*. 1990;27(S1 Suppl):S21–4.
- 2 Patwa HS, Chaudhry V, Katzberg H, Rae-Grant AD, So YT. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2012 Mar;78(13):1009–15.
- 3 Chida K, Nomura H, Konno H, Takase S, Itoyama Y. Recurrent Miller Fisher syndrome: clinical and laboratory features and HLA antigens. *J Neurol Sci*. 1999 Jun;165(2):139–43.
- 4 Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. *Neuroepidemiology*. 2011;36(2):123–33.
- 5 Winer JB. Guillain-Barré syndrome. *BMJ*. 2008 Jul;337:a671.
- 6 Winer JB, Briggs D, Welsh K, Hughes RA. HLA antigens in the Guillain-Barré syndrome. *J Neuroimmunol*. 1988 Apr;18(1):13–6.
- 7 McCombe PA, Csurhes PA, Greer JM. Studies of HLA associations in male and female patients with Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). *J Neuroimmunol*. 2006 Nov;180(1-2):172–7.
- 8 Sauntharajah Y, Nakamura R, Nam JM, Robyn J, Loberiza F, Maciejewski JP, et al. HLA-DR15 (DR2) is overrepresented in myelodysplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome. *Blood*. 2002 Sep;100(5):1570–4.
- 9 Ooi JD, Petersen J, Tan YH, Huynh M, Willett ZJ, Ramarathinam SH, et al. Dominant protection from HLA-linked autoimmunity by antigen-specific regulatory T cells. *Nature*. 2017 May;545(7653):243–7.

- 10 Hu W, Dehmel T, Pirhonen J, Hartung HP, Kieseier BC. Interleukin 23 in acute inflammatory demyelination of the peripheral nerve. *Arch Neurol*. 2006 Jun;63(6):858–64.
- 11 Koga M, Takahashi M, Masuda M, Hirata K, Yuki N. Campylobacter gene polymorphism as a determinant of clinical features of Guillain-Barré syndrome. *Neurology*. 2005 Nov;65(9):1376–81.
- 12 Zhang HL, Zheng XY, Zhu J. Th1/Th2/Th17/Treg cytokines in Guillain-Barré syndrome and experimental autoimmune neuritis. *Cytokine Growth Factor Rev*. 2013 Oct;24(5):443–53.
- 13 Young NS, Calado RT, Scheinberg P. Current concepts in the pathophysiology and treatment of aplastic anemia. *Blood*. 2006 Oct;108(8):2509–19.
- 14 Murakami Y, Kosaka H, Maeda Y, Nishimura J, Inoue N, Ohishi K, et al. Inefficient response of T lymphocytes to glycosylphosphatidylinositol anchor-negative cells: implications for paroxysmal nocturnal hemoglobinuria. *Blood*. 2002 Dec;100(12):4116–22.
- 15 Solomou EE, Rezvani K, Mielke S, Malide D, Keyvanfar K, Visconte V, et al. Deficient CD4+ CD25+ FOXP3+ T regulatory cells in acquired aplastic anemia. *Blood*. 2007 Sep;110(5):1603–6.
- 16 Nakao S, Takamatsu H, Chuhjo T, Ueda M, Shiobara S, Matsuda T, et al. Identification of a specific HLA class II haplotype strongly associated with susceptibility to cyclosporine-dependent aplastic anemia. *Blood*. 1994 Dec;84(12):4257–61.
- 17 Kaya B, Davies CE, Oakervee HE, Silver NC, Gawler J, Cavenagh JD. Guillain Barré syndrome precipitated by the use of antilymphocyte globulin in the treatment of severe aplastic anaemia. *J Clin Pathol*. 2005 Sep;58(9):994–5.
- 18 Bayry J, Mouthon L, Kaveri SV. Intravenous immunoglobulin expands regulatory T cells in autoimmune rheumatic disease. *J Rheumatol*. 2012 Feb;39(2):450–1.
- 19 Asthana P, Vong JS, Kumar G, Chang RC, Zhang G, Sheikh KA, et al. Dissecting the Role of Anti-ganglioside Antibodies in Guillain-Barré Syndrome: an Animal Model Approach. *Mol Neurobiol*. 2016 Sep;53(7):4981–91.