

Epstein-Barr Virus-Associated Hemophagocytic Lymphohistiocytosis and Guillain-Barre Syndrome in a 16-Month-Old Child

Motohiro Matsui, MD^{1,2}, Mariko Shimizu, MD¹, Aya Ioi, MD¹, Azusa Mayumi, MD¹, Kohei Higuchi, MD¹, Akihisa Sawada, MD, PhD¹, Maho Sato, MD, PhD¹, Masahiro Yasui, MD¹, Keiko Yanagihara, MD³, and Masami Inoue, MD¹

Abstract

A 16-month-old girl was diagnosed with Epstein-Barr virus hemophagocytic lymphohistiocytosis and transferred to our hospital on the 58th day of the hemophagocytic lymphohistiocytosis after treatment failure according to the Hemophagocytic Lymphohistiocytosis-2004 protocol. On admission to our hospital, she had a flaccid paralysis of her lower limbs. Nerve conduction studies showed an acute motor axonal neuropathy, and a diagnosis of Guillain-Barre syndrome was established. Intravenous immunoglobulin G was started on the 57th day of the Guillain-Barre syndrome. To date, her neurological recovery is incomplete. For hemophagocytic lymphohistiocytosis, after treatment failure of THP-COP regimen (pirarubicin, cyclophosphamide, vincristine, and prednisone) and 2 courses of ESCAP regimen (etoposide, prednisone, cytarabine, L-asparaginase), we are now in the process of coordinating unrelated umbilical cord blood transplantation. To the best of our knowledge, we report the youngest case of Guillain-Barre syndrome accompanied by Epstein-Barr virus hemophagocytic lymphohistiocytosis. Rapid progression of Guillain-Barre syndrome, the electrophysiological subtype of Guillain-Barre syndrome, and treatment delay possibly led to poor neurological outcome.

Keywords

Guillain-Barre syndrome, Epstein-Barr virus, hemophagocytic lymphohistiocytosis, intravenous immunoglobulin G, acute motor axonal neuropathy

Received August 18, 2015. Received revised September 27, 2015. Accepted for publication October 14, 2015.

Guillain-Barre syndrome is the most common cause of acute flaccid paralysis in children. The incidence is lower in children than in adults, and it is especially rare in children younger than 2 years of age. Major precipitants of Guillain-Barre syndrome include *Campylobacter*, *Cytomegalovirus*, Epstein-Barr virus, *Mycoplasma pneumoniae*, and influenza-like illnesses. However, there are only a few reports of Guillain-Barre syndrome accompanied by hemophagocytic lymphohistiocytosis associated with Epstein-Barr virus infections (Epstein-Barr virus-hemophagocytic lymphohistiocytosis).

We present a case of Guillain-Barre syndrome associated with Epstein-Barr virus-hemophagocytic lymphohistiocytosis. In addition, we analyzed the data of patients with Guillain-Barre syndrome associated with Epstein-Barr virus

infection by conducting a review of the literature using medical databases to investigate the clinicopathological features.

¹ Department of Hematology/Oncology, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

² Department of Pediatrics, National Center for Global Health and Medicine, Tokyo, Japan

³ Department of Neurology, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

Corresponding Author:

Motohiro Matsui, MD, Department of Pediatrics, National Center for Global Health and Medicine, 1-21-1, Toyama, Shinjuku-ku, Tokyo, 162-8655, Japan.
Email: motohiro612@yahoo.co.jp



Case Report

A 16-month-old girl had a 5-day history of fever prior to admission to a local hospital. The diagnosis with Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis was confirmed by hemophagocytosis in her bone marrow sample and a clonally expanded population of Epstein-Barr virus-infected CD8+ T cells. Laboratory data on admission were as follows: white blood cell, $23.9 \times 10^9/L$; hemoglobin, 10.5 g/dL; platelet count, $4.7 \times 10^9/L$; aspartate aminotransferase, 834 IU/L; alanine aminotransferase, 215 IU/L; lactate dehydrogenase, 4340 IU/L; ferritin, 77 597 ng/mL; Epstein-Barr virus capsid antigen immunoglobulin M titer, 20; Epstein-Barr virus capsid antigen immunoglobulin G titer, 40; Epstein-Barr virus-associated nuclear antigen, negative; and Epstein-Barr virus DNA (in peripheral blood), positive (1.3×10^6 copies/ 1.0×10^6 cells). Treatment with dexamethasone (10 mg/m²/day) and oral cyclosporin A (6 mg/kg/day) was promptly initiated. Although a transient improvement in clinical signs was observed on day 15 after hemophagocytic lymphohistiocytosis onset, recurrence of symptoms required the addition of etoposide (150 mg/m²) on day 24 after hemophagocytic lymphohistiocytosis onset. The patient received etoposide once every 3 days on 5 occasions; however, her symptoms recurred on day 56 after hemophagocytic lymphohistiocytosis onset, and she was transferred to our hospital on day 58 after hemophagocytic lymphohistiocytosis onset.

On admission, she was bedridden, had flaccid paralyses in her lower limbs, and could not maintain a sitting position. Although these neurological signs and symptoms were not recognized until the transfer, the mother had noticed symptoms such as her daughter's difficulty in standing up on day 5 after hemophagocytic lymphohistiocytosis onset. Evaluation of muscle strength was conducted according to the Medical Research Council muscle strength grading system; she was given grade 4 and grade 2 in the upper and lower extremities, respectively. Deep tendon reflexes were absent throughout. Cerebrospinal fluid examination on admission revealed 13 mg/dL of protein and 66 mg/dL of glucose, without an increase in cell numbers, and the patient was Epstein-Barr virus DNA negative. The antiganglioside antibodies in cerebrospinal fluid, such as immunoglobulin G and immunoglobulin M for GM1, GM2, GM3, GD1a, GD3, GalNAc-GD1a, GQ1b, GD1b, GT1b, and Gal-C, were all negative. Nerve conduction studies showed that the amplitude of the compound muscle action potential was severely decreased, and the pattern was almost compatible with acute motor axonal neuropathy. A diagnosis of Guillain-Barre syndrome was reached based on the clinical features and nerve conduction studies. Treatment with intravenous immunoglobulin G (0.4 g/kg/day for 5 days) was commenced on day 62 after hemophagocytic lymphohistiocytosis onset. On day 88 after hemophagocytic lymphohistiocytosis onset, the patient was able to maintain a sitting position, muscle strength had improved from grade 2 to grade 3, and the nerve conduction study pattern had normalized. However, to date, her neurological

recovery is incomplete, and she is still unable to pull herself up.

For hemophagocytic lymphohistiocytosis, the patient received a THP-COP treatment regimen (pirarubicin 25 mg/m² on days 1-2, cyclophosphamide 750 mg/m², and vincristine 1.5 mg/m² on day 1, and prednisone 50 mg/m² on days 1-5). After this treatment, the Epstein-Barr virus copy number in her peripheral blood slightly decreased from 1×10^6 copies/mL on admission to 2×10^5 copies/mL. To reduce the Epstein-Barr virus copy number, 2 courses of ESCAP regimen (etoposide 150 mg/m² on day 1, prednisone 30 mg/m² on days 6-9, cytarabine 1.5 g/m² \times 2 on days 1-5, and L-asparaginase 6000 IU/m² on days 5-9) were commenced on days 88 and 109 after hemophagocytic lymphohistiocytosis onset. The Epstein-Barr virus copy number increased after the second course of ESCAP, thus we are now in the process of coordinating unrelated umbilical cord blood transplantation. No correlation was detected between Epstein-Barr virus copy number and the degree of neurological symptoms.

Discussion

Epstein-Barr virus is a widely disseminated herpesvirus with approximately 90% to 95% of adults showing seropositivity. This virus sometimes causes serious complications including hemophagocytic lymphohistiocytosis and Guillain-Barre syndrome; the present case had a combination of these 2 rare complications.

As far as we investigated, PubMed database included 12 cases who had Guillain-Barre syndrome with proven Epstein-Barr virus infection. Of the 12 cases, only 2 had Epstein-Barr virus-hemophagocytic lymphohistiocytosis. Seven of the 12 cases achieved complete neurological recovery, 4 died because of Epstein-Barr virus infection, and only 1 resulted in a mild neurological sequela.

This is the first report of such a case in a child younger than 2 years of age. Childhood Guillain-Barre syndrome is a rare disease with an incidence of 0.5 to 2 cases per 100 000 children younger than 18 years old^{1,2} and is especially rare in children younger than 2 years old. Although the reason for its rarity in younger children is unknown, one report has suggested that the difficulty in conducting a complete series of neurological examinations has resulted in underdiagnosis among the younger population.³

The presence of Epstein-Barr virus infection in Guillain-Barre syndrome is relatively rare. Clarence et al⁴ reported that the incidence rate of Epstein-Barr virus infection in Guillain-Barre syndrome was 0.36%. In our review, only 2 children, both older than 2 years, had Guillain-Barre syndrome accompanied by Epstein-Barr virus infection (Table 1; cases 2 and 7). On the other hand, Guillain-Barre syndrome accompanied by Epstein-Barr virus-hemophagocytic lymphohistiocytosis was rare based on our review, and only 2 reports have been published. We believe that the case reported here represents the youngest known patient with

Table 1. Characteristics of the Patients With Guillain-Barre Syndrome Accompanied by Epstein-Barr Virus Infection.^a

Case	Age, Years/ Gender	EBV Infection	Subtype	Therapy	Outcome	Neurological Outcome	Author (Year)
1	78/M	HLH	Unknown	IVIG + IVMP	CR	CR at 3 months	Kaneko et al (1997) ¹⁰
2	11/M	HLH	AIDP	–	Died	–	De Armas et al (2004) ¹¹
3	47/M	LPD	AMAN	IVIG	CR	CR at 9 months	Hattori et al (2014) ¹²
4	29/M	IM	AIDP	PE	CR	CR at 18 days	Kennedy et al (2013) ¹³
5	72/M	CAEBV	Unknown	IVIG	Died	–	Takahashi et al (2005) ¹⁴
6	46/M	Reactivation after BMT	Unknown	–	Died	–	Bitan et al (2004) ¹⁵
7	21M	NS	Unknown	IVIG	CR	CR at 3 months	Young et al (2014) ¹⁶
8	63/M	NS	AIDP	PE	CR	CR at 3 months	Masajtis-Zagajewska et al (2012) ¹⁷
9	491M	NS	AIDP	IVIG	CR	CR at 1 month	Young et al (2008) ¹⁸
10	211M	NS	Unknown	–	Died	–	Ringelstein et al (2012) ¹⁹
11	17/F	IM	Unknown	IVIG + IVMP	CR	CR at 2 months	Hojberg et al (2005) ²⁰
12	18/M	IM	AMSAN AIDP	PE	CR	Weak ankle dorsiflexion at 2 months	Gavin et al (1996) ²¹
13	1/F	EBV-HLH	AMAN	IVIG	–	Unable to stand up at 4 months	Present case

Abbreviations: LPD, lymphoproliferative disease; IM, infectious mononucleosis; CAEBV, chronic active Epstein-Barr virus infection; NS, not specified; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; IVIG, intravenous immunoglobulin G; PE, plasma exchange; IVMP, pulsed methylprednisolone; CR, complete response; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; BMT, bone marrow transplant; AMSAN, acute motor and sensory axonal neuropathy.

^a N = 13.

Guillain-Barre syndrome accompanied by Epstein-Barr virus-hemophagocytic lymphohistiocytosis.

Generally, children with Guillain-Barre syndrome have a faster and better recovery than adults.⁵ Roodbol et al reported that all 37 pediatric patients with Guillain-Barre syndrome were able to walk independently within 1 year of disease onset, including those who were severely affected during the acute stage of the disease.⁶ In our review, only 1 of the 12 patients treated with plasma exchange or intravenous immunoglobulin G had a residual sequela. However, the child in the present case still has incomplete neurological recovery 4 months after the disease onset. We have 3 theories as to why this case is still affected by sequela. First, there is the possibility that nerve recovery was delayed because of the Guillain-Barre syndrome subtype. Nagasawa et al reported that cases with acute motor axonal neuropathy showed delayed recovery more frequently than acute inflammatory demyelinating polyneuropathy cases.⁷ Second, there is a possibility that a rapid progress in symptoms resulted in a poor prognosis. Although data regarding prognostic indicators of Guillain-Barre syndrome in children are limited, some reports suggest that progression to maximal weakness in less than 10 days constitutes a greater risk of long-term deficits (odds ratio, 1.8; 95% confidence interval, 1.06-3.67; $P = .03$).⁸ Third, the delay in treatment in our case could have resulted in incomplete nerve recovery.

The guidelines from the American Academy of Neurology recommend that intravenous immunoglobulin G for nonambulatory adult patients with Guillain-Barre syndrome should start within 2 to 4 weeks of the onset of neuropathic symptoms because the outcome is thought to be better for this group.⁹ In our case, muscle weakness symptoms progressed rapidly, and intravenous immunoglobulin G was commenced 2 months

after the onset of neuropathic symptoms. It can be that the cause of the sequela in this case was due to the rapid progression of symptoms and the delay in treatment.

Both Epstein-Barr virus-hemophagocytic lymphohistiocytosis and Guillain-Barre syndrome can be fatal diseases. If they coexist, the balance of medical care in treating both diseases is very important. Treatment for hemophagocytic lymphohistiocytosis does not work for Guillain-Barre syndrome and vice versa. If a patient has neurological symptoms, there should be no hesitation in using invasive diagnostic procedures, such as nerve conduction study.

To the best of our knowledge, the authors report the youngest case of Guillain-Barre syndrome accompanied by Epstein-Barr virus-hemophagocytic lymphohistiocytosis. Rapid progression of Guillain-Barre syndrome, the electrophysiological subtype of Guillain-Barre syndrome, and treatment delay possibly led to poor neurological prognosis.

Author Contributions

Authors are directly responsible for patients' care, medical records, writing, and editing.

Ethical Approval

Informed consent was obtained from the patients' parents.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was

supported in part by Grants-in-Aid for Research from the National Center for Global Health and Medicine (26A-201).

References

1. Agrawal S, Peake D, Whitehouse WP. Management of children with Guillain-Barre syndrome. *Arch Dis Child Educ Pract Ed*. 2007;92(6):161-168.
2. Winner SJ, Evans JG. Age-specific incidence of Guillain-Barre syndrome in Oxfordshire. *Q J Med*. 1990;77(284):1297-1304.
3. Pier DB, Hallbergson A, Peters JM. Guillain-Barre syndrome in a child with pain: lessons learned from late diagnosis. *Acta Paediatr*. 2010;99(10):1589-1591.
4. Clarence C.T, Sarha J.O, Irene P, Amir I, Andrew H, Laura C.R. Guillain-Barre syndrome and Preceding infection with campylobacter, influenza and Epstein-Barr virus in the general practice research database. *PLoS One*. 2007;2(4):e344.
5. Korinthenberg R, Monting JS. Natural history and treatment effects in Guillain-Barre syndrome: a multicenter study. *Arch Dis Child*. 1996;74(4):281-287.
6. Roodbol J, de Wit MC, Aarsen FK, Catsman-Berrevoets CE, Jacobs BC. Long term outcome of Guillain-Barre syndrome in children. *J Peripher Nerv Syst*. 2014;19(2):121-126.
7. Nagasawa K, Kuwabara S, Misawa S, et al. Electrophysiological subtypes and prognosis of childhood Guillain-Barre syndrome in Japan. *Muscle Nerve*. 2006;33Z(6):766-770.
8. Vajsar J, Fehlings D, Stephens D. Long-term outcome in children with Guillain-Barre syndrome. *J Paediatr*. 2003;142(3):305-309.
9. Hughes RA, Wijdicks EF, Barohn R, et al. Practice parameter: immunotherapy for Guillain-Barre syndrome: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2003;61(6):736-740.
10. Kaneko M, Kuwabara S, Hatakeyama A, Fukutake T, Hattori T. Guillain-Barre and virus-associated hemophagocytic syndrome contracted simultaneously following Epstein-Barr viral infection. *Neurology*. 1997;49:870-871.
11. De Armas R, Sindou P, Gelot A, Routon M.C, Ponsot G, Vallat J.M. Demyelinating peripheral neuropathy associated with hemophagocytic lymphohistocytosis. *An immuno-electron microscopic study*. *Acta Neuropathol*. 2004;108:341-344.
12. Hattori T, Arai A, Yokota T, Imadome K, Tomimitsu H, Miura O, Mizusawa H. Immune-mediated Neuropathy with Epstein-Barr virus-positive T-cell Lymphoproliferative Disease. *Intern Med*. 2015;54:69-73.
13. Kennedy M, Apostolova M. A rare case of infectious mononucleosis complicated by Guillain-Barre syndrome. *Neurol Intern*. 2013;5:20-22.
14. Takahashi K, Kunishige M, Shinohara M, Kubo K, Inoue H, Yoshino H, Asano A, Honda S, Matsumoto T, Mitsui T. Guillain-Barre syndrome and hemophagocytic lymphohistocytosis in a patient with severe chronic active Epstein-Barr virus infection syndrome. *Clin Neurol Neurosurg*. 2005;108:80-83.
15. Bitan M, Reuven Or, Michael Y.S, Nurth M, Igor B.R, Niveen S, Klaus M.W, Simcha S, Esther S, Shimon S, Dana G.W. Early-Onset Guillain-Barre Syndrome Associated with Reactivation of Epstein-Barr Virus Infection after Nonmyeloablative Stem Cell Transplantation. *Clin Infect Dis*. 2004;39:1076-8.
16. Young II R. Overlapping Guillain-Barre syndrome and Bikerstaff's brainstem encephalitis associated with Epstein Barr virus. *Korean J Paediatr*. 2014;57:457-460.
17. Masajtis-Zagajewska A, Katarzyna M, Alina M-T, Ilona K, Michal N. Guillain-Barre syndrome in the course of EBV infection after kidney transplantation - a case report. *Ann Transplant*. 2012;17:133-137.
18. Young AJ, Yoon B, Kim J S, Song I U, Lee K S, Kim Y I. Guillain-Barre Syndrome with Optic Neuritis and Focal Lesion in the Central White Matter Following Epstein-Barr Virus Infection. *Intern Med*. 2008;47:1539-1542.
19. Ringelstein EB, Sobczak H, Preifer B, Hacke W. Polyradiculomeningoencephalitis caused by Epstein-Barr virus infection—description of a case with fatal outcome. *Forsch Neurol Psychiatr*. 1984; 52:73-82.
20. Hojberg L, Sondergard E, Pedersen C. A case of Epstein-Barr virus infection complicated with Guillain-Barre syndrome involving several cranial nerves. *Case Reports*. 2005; 522-524.
21. Gavin C, Langan Y, Hutchinson M. Cranial and peripheral neuropathy due to Epstein-Barr virus infection. *Postgrad Med*. 1997; 73:419-432.