MERS associated with bacterial translocation in a pediatric patient with congenital portal vein hypoplasia: A case report

GEORGE IMATAKA[1], TAKESHI YAMAGUCHI[2], JUNPEI ISHII[1], KEI OGINO[2], KENTARO OKAMOTO[2,3], TAKASHI TSUCHIOKA[2] and SHIGEMI YOSHIHARA[1]

Departments of [1]Pediatrics and [2]First Surgery, Dokkyo Medical University, Shimotsuga, Tochigi 321-0293; [3]Department of Pediatric Surgery, Tokyo Medical and Dental University, Tokyo 113-8510, Japan

Received October 6, 2017; Accepted December 8, 2017

DOI: 10.3892/etm.2018.6532

Abstract. A case of mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) in a female child who developed bacterial translocation from a congenital portal vein hypoplasia is reported. The patient was diagnosed as having portal hypertension after examinations and laboratory results showing splenomegaly and thrombocytopenia at the age of 1 year. The patient required three endoscopic variceal ligation (EVL) surgeries before the age of 9 due to development of multiple esophageal varices. After the second and third EVL procedures, she developed septicemia, possibly due to bacterial translocation associated with the administration of general anesthesia. The day after the third EVL, the patient presented with high fever and neurological disturbances (altered consciousness). Magnetic resonance imaging detected abnormal intensities in the corpus callosum ampulla and cerebral white matter, which suggested a diagnosis of MERS type 2. Considering this clinical course, the possible association between bacterial translocation and MERS in a patient with congenital portal vein hypoplasia and portal hypertension is discussed.

Introduction

Mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) is a type of acute encephalitic encephalopathy as reported by Tada *et al* (1). The characteristic magnetic resonance imaging (MRI) findings of MERS include reversible lesions of the splenium of the corpus callosum that resolved spontaneously within one week in most cases (2). In recent years, diffusion weighted images (DWIs) of MRI have become widespread, and reports have increased on incidences of MERS related to various conditions. The clinical course of MERS is generally mild, when compared to other types of acute encephalopathy, and it depends on the severity of the subjacent condition. The pathogenesis of MERS has been known to involve a variety of different mechanisms and includes cases associated with the use of anti-epileptic drugs (3,4), cases accompanying acute mountain sickness (5), and others associated to microbial infections (mycoplasma (6), legionella (7), dengue fever (8), rubella (9), rotavirus (10), HHV-6 (11), Influenza virus type A (12), and others). Thus, MERS is recognized as a unique clinico-radiological encephalitis/encephalopathy syndrome associated with diverse pathological conditions. However, to the best of our knowledge, this is the first instance wherein bacterial translocation has been implicated as a causative mechanism. Herein, we report the case of a 9-year-old girl who had complicated esophageal varices due to congenital portal vein hypoplasia and developed a bacterial infection with abdominal pain and neurological abnormalities that led to a diagnosis of MERS.

Case report

Our pediatric patient was born following a normal delivery at 37 weeks of gestation. Her birth height was 43.3 cm and her weight was 2,090 g. There were no delays in motor development and the girl started walking at the age of 1. No family history of major diseases was reported.

One year after her birth, the girl was reported to suffer from frequent epistaxis episodes. Medical examinations performed at the local hospital showed she had thrombocytopenia and splenomegaly. She was referred to our university hospital at the age of 1 year and 3 months; X-ray images showed evidence of an expansion of the mediastinum, which led us to suspect the presence of a mediastinal tumor. A chest computed tomography (CT) scan revealed a low-density area in the hepatic portal section, and a tentative diagnosis of portal hypertension was made. After that, the patient underwent abdominal ultrasound and contrast CT examinations, and abnormalities of the portal vein running through the liver were recognized. Multiple esophageal varices were also confirmed by upper gastrointestinal contrast radiographic images. Overall, the

Correspondence to: Dr George Imataka, Department of Pediatrics, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Shimotsuga, Tochigi 321-0293, Japan
E-mail: geo@dokkyomed.ac.jp

Key words: mild encephalitis/encephalopathy with a reversible splenial lesion, bacterial translocation, endoscopic variceal ligation, congenital portal vein hypoplasia, portal hypertension

patient was diagnosed as having idiopathic portal hypertension caused by congenital portal hypoplasia.

At 3 years of age, contrast CT examination showed exacerbation of the esophageal varices from the lower portion of the esophagus to the cardia of the stomach. The portal vein was undergoing a cavernous transformation from the splenoportal junction. The images revealed a splenic vein aneurysm. Additionally, the left kidney was atrophic due to the progressing splenomegaly. Therefore, a pediatric surgeon performed an endoscopic variceal ligation (EVL) surgery at multiple sites that were deemed as prone to bleeding.

A second EVL surgery for recurrent esophageal varices was performed under general anesthesia when the patient was 6 years and 8 months. The day after the EVL surgery, the girl experienced a sudden high fever (>40˚C). Paralysis of the intestinal tract due to general anesthesia and the existing portal vein hypoplasia were suspected as resulting in secondary bacterial translocation and sepsis. The blood culture test collected from the elbow vein produced a negative result. An attempt to obtain blood directly from the portal vein proved impossible. Nevertheless, a course of antibiotics and gamma globulin therapy were promptly administered and the infectious symptoms subsided.

Later, at the age of 9 years and 6 months, the patient underwent a third EVL surgery under general anesthesia once again for esophageal varices. This time, cephem antibiotics (ceftriaxone sodium hydrate; CTRX) were prescribed prophylactically and immediately after the surgical procedure. Nevertheless, the next day after the EVL surgery, the girl developed a 40˚C fever. She was hospitalized in the city hospital but her consciousness level reduced by the evening of the same day. Thus, she was transferred to our university hospital. Blood examinations showed the following values: White blood cells $3{,}200 \times 10^9$/l, hemoglobin 10.4 g/dl, Plt $2.3 \times 10^4/\mu$l, sodium 130 mEq/l, CRP 7.39 mg/dl, and procalcitonin 26.34 ng/ml. Sepsis and acute encephalopathy due to bacterial translocation after the EVL surgery were suspected. The cell count of cerebral spinal fluid collection was 42/μl. A head CT showed no remarkable changes. Her MRI images, nonetheless, revealed abnormal signal intensities mainly at the splenium of the corpus callosum and both sides of white matter using contrast (Fig. 1). So the patient was diagnosed as having a MERS type 2, which was probably precipitated by bacterial translocation. The antibiotic treatment with CTRX was switched to penem (panipenem; PAPM/BP) and 5 days of gamma globulin therapy with 3 days of steroid pulse treatment. After 24 h of the last treatment dosage, the fever prevailed but at a lower temperature. On the second day after the aforementioned treatments, DWIs of MRI showed marked improvement (Fig. 1), a finding that was in agreement with the typical course of MERS. Nevertheless, many abnormal spots suspected to be due to micro-bleeding were apparent (Fig. 2). On the third day after the treatment, her neurological symptoms and fever had completely disappeared. Regarding the publication of this case report, the patient's parents consented in advance to the formal form prepared by the Ethics Organization Committee of Dokkyo Medical University Hospital (Tochigi, Japan).

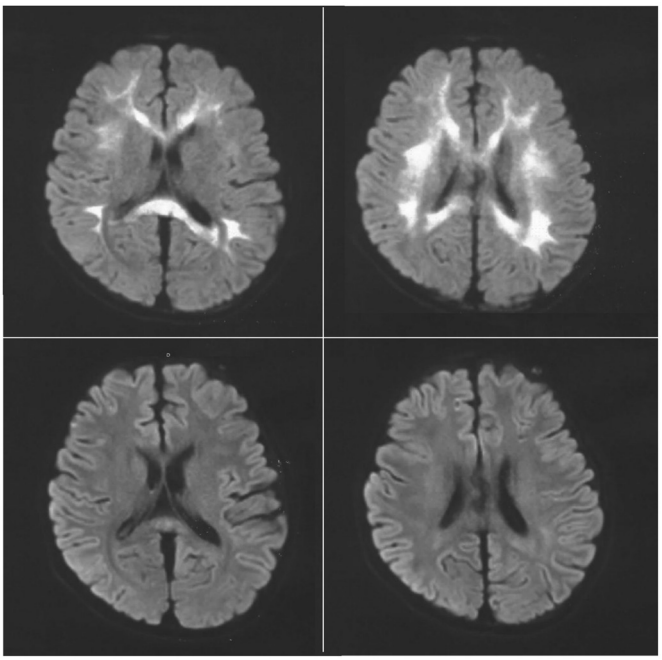

Figure 1. Brain MRI upon hospital admission. Top panels: (DWI) of abnormal signal intensities from MRI were mainly in the corpus callosum and in both sides of the white matter before treatment. Lower panels: DWI signal intensities on MRI improved two days after treatment. DWI, diffusion weighted image; MRI, magnetic resonance imaging.

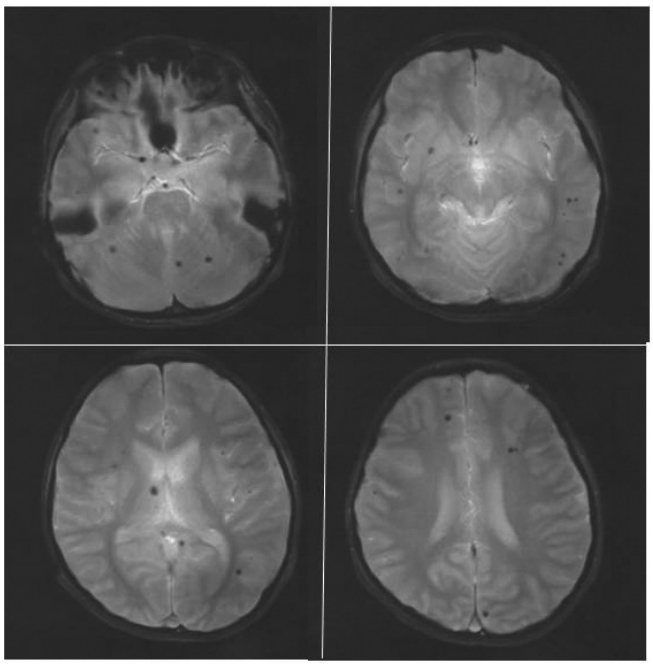

Figure 2. Brain magnetic resonance imaging after MERS resolution. Microbleeding of small vessels was recognized following the fat suppression method of short T1 weighted inversion recovery images after treatment. MERS: mild encephalitis/encephalopathy with a reversible splenial lesion.

Discussion

The clinical course of this pediatric case is very interesting. Initially, the patient manifested symptoms of portal hypertension due to congenital portal defects. Between infancy and childhood, formation of a collateral circulation pathway to compensate for portal vein deficits was observed, complicating the situation with dangerous esophageal varices from the left gastric vein. In addition, pancytopenia accompanied by marked reduction of platelet cells was

observed as a result of spleen hyperfunction. Under such circumstances, any gastroenteritis is likely to bring bacteria and toxic substances from the intestinal tract directly into the general circulation system, which can lead to septicemia and encephalopathy from the translocated bacteria. On the other hand, in cases where bacterial translocation is suspected and in cases where antibiotics are already being administered, the causative bacteria are rarely detected.

In the course of our case, fever and abdominal pain, seen as symptoms of gastroenteritis, evolved to develop neurological speech disturbances with altered consciousness. An emergency MRI then led to the diagnosis of MERS. The clinical course of MERS has been previously reported to include a febrile state with alterations of speech and consciousness (13). These symptoms are considered part of febrile derilium (14). However, the fever in our patient was more consistent, one having an infectious origin due to its onset timing and the results of the initial blood tests at hospitalization, which were consistent with a septicemia. The possibility of disseminated intravascular coagulation (DIC) syndrome was difficult to rule out in our patient due to the impossibility of distinguishing it from the original low platelet counts and pancytopenia from the underlying spleen hyperactivity. The treatment chosen for the patient included antibiotics and gamma globulin therapy and steroid pulses for MERS with sepsis and possible DIC syndrome. The diagnosis of MERS was further confirmed by the fast improvement of splenial abnormalities on the MRI re-examination after 2 days of treatment. And the efficacy of the administered treatment was clear with a complete resolution of the patient's symptoms 3 days after treatment.

Bacterial translocation occurs when abnormal proliferation of intestinal bacteria coupled with impairment of the intestinal mucosa defense function leads to an extremely serious systemic infection. In those instances, intestinal bacteria penetrate the broken barrier of intestinal mucosal epithelium and migrate to the whole body via blood and lymph flow. Such cases generally ensue on fasting patients with acute gastroenteritis or some kind of intestinal chronic disease that leads to abnormally slow intestinal flow, accumulation of bacteria, and altered defense function of the intestinal mucosa. In our patient, portal hypertension and slowed intestinal tract movements due to anesthesia probably led to edema of the intestinal mucosa and deterioration of the lymphatic vessel flow, which together allowed the translocation of intestinal bacteria that ultimately reached the central nervous system. Recent advances in the pathogenesis mechanisms of bacterial translocation point to the effects of direct invasion of bacterial cells throughout the body as well as severe inflammatory reactions caused by inflammatory cytokines released during phagocytosis in the broken intestinal mucosa. As such, there have been reports of MERS from bacteremia with toxic shock syndrome (15), and MERS associated with acute focal bacterial nephritis caused by *Enterococcus faecalis* related to marked elevation of interleukin 6 (16). Our case of MERS is also related to bacterial infection triggered by bacterial translocation, which caused symptoms of bacteremia or sepsis and acute encephalopathy.

The clinical course of MERS varies among patients, and a clear mechanism of onset has not yet been elucidated. Nevertheless, it is interesting to note that severe bacterial infections due to bacterial translocation may be at play in the multiple cases of MERS in childhood associated with viral infections that run a clinical course similar to the one described here. We believe that our report represents a model case of bacterial translocation leading to MERS.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GI, TY, JI, KOg, KOk and TT designed the study and drafted the manuscript. GI, JI and SY collected the clinical and imaging data and analyzed the serological data. TY, Kog, Kok and TT operated and collected surgical and anatomical information of the patient. SY collected information on the medical history of the patient, interpreted blood test data and decided the fluid therapy treatment. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Regarding the publication of this case report, the patient's parents consented in advance to the formal form prepared by the Ethics Organization Committee of Dokkyo Medical University Hospital (Tochigi, Japan).

Patient consent for publication

Consent was obtained from the parents of the patient for publication of data.

Competing interests

The authors declare that they have no competing interests.

References

1. Tada H, Takanashi J, Barkovich AJ, Oba H, Maeda M, Tsukahara H, Suzuki M, Yamamoto T, Shimono T, Ichiyama T, *et al*: Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. Neurology 63: 1854-1858, 2004.
2. Takanashi J, Hirasawa K and Tada H: Reversible restricted diffusion of entire corpus callosum. J Neurol Sci 247: 101-104, 2006.
3. Kim SS, Chang KH, Kim ST, Suh DC, Cheon JE, Jeong SW, Han MH and Lee SK: Focal lesion in the splenium of the corpus callosum in epileptic patients: Antiepileptic drug toxicity? AJNR Am J Neuroradiol 20: 125-129, 1999.
4. Maeda M, Shiroyama T, Tsukahara H, Shimono T, Aoki S and Takeda K: Transient splenial lesion of the corpus callosum associated with antiepileptic drugs: Evaluation by diffusion-weighted MR imaging. Eur Radiol 13: 1902-1906, 2003.

5. Kallenberg K, Bailey DM, Christ S, Mohr A, Roukens R, Menold E, Steiner T, Bärtsch P and Knauth M: Magnetic resonance imaging evidence of cytotoxic cerebral edema in acute mountain sickness. J Cereb Blood Flow Metab 27: 1064-1071, 2007.
6. Yuan ZF, Shen J, Mao SS, Yu YL, Xu L, Jiang PF, Gao F and Xia ZZ: Clinically mild encephalitis/encephalopathy with a reversible splenial lesion associated with Mycoplasma pneumoniae infection. BMC Infect Dis 16: 230, 2016.
7. Tomizawa Y, Hoshino Y, Sasaki F, Kurita N, Kawajiri S, Noda K, Hattori N, Amemura-Maekawa J, Kura F and Okuma Y: Diagnostic utility of splenial lesions in a case of legionnaires' disease due to legionella pneumophila serogroup 2. Intern Med 54: 3079-3082, 2015.
8. Saito N, Kitashouji E, Kojiro M, Furumoto A, Morimoto K, Morita K and Ariyoshi K: A case of clinically mild encephalitis/encephalopathy with a reversible splenial lesion due to dengue fever. Kansenshogaku Zasshi 89: 465-469, 2015 (In Japanese).
9. Jinnai A, Kikuchi T, Ishikawa M, Nishimura Y, Shibata K and Sakura H: A case of rubella encephalitis presenting as clinically mild encephalitis/encephalopathy with a reversible splenial lesion. Rinsho Shinkeigaku 54: 668-670, 2014 (In Japanese).
10. Kobata R, Tsukahara H, Nakai A, Tanizawa A, Ishimori Y, Kawamura Y, Ushijima H and Mayumi M: Transient MR signal changes in the splenium of the corpus callosum in rotavirus encephalopathy: Value of diffusion-weighted imaging. J Comput Assist Tomogr 26: 825-828, 2002.
11. Hatanaka M, Kashiwagi M, Tanabe T, Nakahara H, Ohta K and Tamai H: Overlapping MERS and mild AESD caused by HHV-6 infection. Brain Dev 37: 334-338, 2015.
12. Takanashi J, Tada H, Kuroki H and Barkovich AJ: Delirious behavior in influenza is associated with a reversible splenial lesion. Brain Dev 31: 423-426, 2009.
13. Hoshino A, Saitoh M, Oka A, Okumura A, Kubota M, Saito Y, Takanashi J, Hirose S, Yamagata T, Yamanouchi H and Mizuguchi M: Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. Brain Dev 34: 337-343, 2012.
14. Takanashi J, Takahashi Y, Imamura A, Kodama K, Watanabe A, Tominaga K, Muramatsu K and Barkovich AJ: Late delirious behavior with 2009 H1N1 influenza: Mild autoimmune-mediated encephalitis? Pediatrics 129: e1068-e1071, 2012.
15. Kosami K, Kenzaka T, Sagara Y, Minami K and Matsumura M: Clinically mild encephalitis/encephalopathy with a reversible splenial lesion caused by methicillin-sensitive Staphylococcus aureus bacteremia with toxic shock syndrome: A case report. BMC Infect Dis 16: 160, 2016.
16. Kometani K, Kawatani M, Ohta G, Okazaki S, Ogura K, Yasutomi M, Tanizawa A and Ohshima Y: Marked elevation of interleukin 6 in mild encephalopathy with a reversible splenial lesion (MERS) associated with acute forcal bacterial nephritis caused by *Enterococcus faecalis*. Brain Dev 36: 551-553, 2014.