CASE REPORT

Two pediatric cases of severe hemophilia A in which emicizumab prophylaxis failed to prevent traumatic extra-articular hemorrhage

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Abstract
Emicizumab reduces bleeding episodes in patients with severe hemophilia A (PwHA). Little information is available on hemostatic management of severe traumatic hemorrhages in emicizumab-treated pediatric PwHA. We assessed therapeutic efficacy and global coagulation potentials in two pediatric cases of emicizumab-treated pediatric PwHA with intracranial or retroperitoneal iliopsoas hemorrhage. A modified clot waveform analysis (CWA) triggered by mixtures of tissue factor and ellagic acid was used to assess coagulant potentials, and maximum coagulant velocity (Ad|min|1) was calculated. One patient with intracranial hemorrhage was treated with continuous infusions of recombinant factor VIII (rFVIII) at a dose of 4–4.6 IU/kg/hr for 9 days, followed by bolus infusion at 66 IU/kg/day for 2 days and 33 IU/kg/day for an additional 2 days. The Ad|min|1 was increased from 5.5 (at baseline) to 7.0–8.1 under concomitant treatment and maintained within or near normal range (IQR; 6.9–7.7). The other patient with retroperitoneal iliopsoas hemorrhage received bolus infusions of rFVIII at 50 IU/kg/day for 20 days and every-other-day infusion of rFVIII for 8 days. The Ad|min|1 was increased from 5.2 (at baseline) to 5.8–6.8 under concomitant treatment and maintained within the normal range. We successfully managed a treatment plan for severe traumatic bleeding in emicizumab-treated pediatric PwHA using modified CWA.

Keywords Hemophilia A · Factor VIII · Severe traumatic bleeding · Bispecific antibody · Hemostatic monitoring

Introduction
Hemophilia A (HA) results from a deficiency or defect in factor (F)VIII procoagulant protein and is the most common severe congenital bleeding disorder. Patients with HA (PwHA) present with notable hemorrhage from early childhood and repeated bleeding episodes, including joint and/or intramuscular bleeding [1]. It is well known that life-threatening bleeding in PwHA is a risk factor for early death and is significantly associated with morbidity [2]. Several previous studies have reported that intracranial hemorrhage often results in mortality, severe sequelae, and a high rate of subsequent development of anti-FVIII inhibitory alloantibodies in survivors [3, 4]. Iliopsoas hemorrhages often compress the femoral nerve due to the expanding lesion in the muscle and sometimes develop into compartment syndrome or pseudo-tumors [5]. Retroperitoneal hematoma also often leads to a serious and life-threatening bleeding condition with challenging hemostatic management [6–8].

Emicizumab (Hemlibra®; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) is a recombinant, bispecific monoclonal antibody (mAb) that binds to FIX/activated FIX (FIXa) and FX/FXa, and mimics FVIIIa cofactor activity in the tenase complex [9, 10]. Real-world data on emicizumab use have suggested its safety and demonstrated that it is well tolerated in adult and pediatric PwHA [11–14]. However, there are few reports on the clinical course and therapeutic management of emicizumab-treated PwHA with severe traumatic
bleeding such as intracranial, iliopsoas, and retroperitoneal hemorrhages.

**Case presentation**

We report the clinical outcomes and assessment of coagulation potentials using clot waveform analysis (CWA) during the clinical therapeutic course for one pediatric patient with intracranial hemorrhage and one with both iliopsoas and retroperitoneal hemorrhages, despite receiving emicizumab prophylaxis. In the modified CWA, the minimum value of the 1st derivative (|min1|) was calculated as an indicator of the maximum velocity of coagulation. Adjust|min1| (Ad|min1|) was re-defined as the maximum coagulation velocity obtained in the 1st derivative of adjusted-clot waveform [15]. FVIII activity (FVIII:C) after the addition of two anti-emicizumab antibodies was measured [16]. Emicizumab concentration in patients’ plasmas was also investigated using a modified one-stage clotting assay [17]. This study was approved by the Medical Research Ethics Committee of Nara Medical University (No. 2503), and blood samples were collected after obtaining informed consent in accordance with the ethical guidelines of our university.

**Case 1: intracranial hemorrhage**

One patient had the first intracranial hemorrhage 6 days after birth and was diagnosed with severe HA. He underwent craniotomy for intracranial hemorrhage and received recombinant (r)FVIII supplementation for perioperative treatment. He had intracranial hemorrhage again at the age of 2 months, and an FVIII inhibitor was detected (4.4 BU/mL). Immune tolerance induction therapy was initiated with an rFVIII product (200 IU/kg, × 3/week), and tolerance was achieved after 9 months. Since starting emicizumab prophylaxis at 3.0 mg/kg every 2 weeks at the age of 4 years, he did not experience breakthrough bleeding. Concerning the sequelae of intracranial hemorrhage, although he had hydrocephalus complicated with epilepsy, his epilepsy was well controlled by oral antiepileptic drugs. He always wore headgear to protect his head from injury. At the age of 6 years, after he had a head contusion, he started vomiting and gradually became inactive. On the third day after injury, he visited the previous hospital, and computed tomography (CT) of the brain revealed intracranial hemorrhage. He immediately received a bolus infusion of rFVIII (33 IU/kg) and was transferred to our hospital to manage the intracranial hemorrhage. On admission, his consciousness was clear and vital signs were normal, but he developed malaise, nausea, and headache. No cases of paralysis or pupillary inequality were observed. A blood examination revealed no anemia or thrombocytopenia. Brain CT revealed that the hemorrhage size did not further increase, and no midline shift was found (Fig. 1). After administering a bolus infusion of rFVIII at 33 IU/kg, we chose the conservative therapeutic plan with continuous infusion of rFVIII. The patient received a constant infusion of rFVIII 4–4.6 IU/kg/hr for 9 days, and his symptoms gradually disappeared on the day of hospitalization. A follow-up CT (on day 10) showed hematoma absorption. Subsequently, he was switched to a bolus infusion of rFVIII at 33 IU/kg × 2/day for 2 days and 33 IU/kg/day for an additional 2 days. He showed no recurrence of symptoms and was discharged on day 14.

We assessed the hemostatic potential in this case (Fig. 2). Since he had received a single infusion of rFVIII (33 IU/kg) at the previous hospital, Ad|min1| and emicizumab concentration in his plasma after in vitro addition of purified FVIII inhibitor IgG to neutralize FVIII:C were measured. The Ad|min1| was 5.5 and the plasma concentration of emicizumab was 30 µg/mL, indicating the efficacy of emicizumab prophylaxis [17, 18]. The continuous infusion of the rFVIII at 4–4.6 IU/kg/hr maintained the FVIII:C above 50 IU/dL, and the Adimin1 increased to 7.0–8.1, in the normal range (IQR: 6.9–7.7 [19]). As the bolus dose of rFVIII was gradually decreased, the FVIII:C and Adimin1 values approached to baseline. No FVIII inhibitors were detected during hospitalization.

![Fig. 1 Time course of change in brain CT findings in Case 1. The brain CT shows an improvement in intracranial hemorrhage](image-url)
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Case 2: iliopsoas and retroperitoneal hemorrhage

The other patient had an intracranial hemorrhage at the age of 9 days and was diagnosed with severe HA. He underwent craniotomy under hemostatic management with rFVIII product. The FVIII inhibitor titer was detected (0.75 BU/mL) at the age of 3 months but spontaneously disappeared. Since starting emicizumab prophylaxis at 3.0 mg/kg once every 2 weeks at the age of 1.5 years, he experienced no breakthrough bleeding. At the age of 6 years, he fell off his bicycle and hit the left side of his abdomen. On day 4 after injury, he had severe abdominal pain and restriction of his left knee, and he was admitted to our hospital. His blood examination showed no anemia or thrombocytopenia but a markedly shortened aPTT value (< 23.0 s). Abdominal CT revealed severe left retroperitoneal and iliopsoas muscle hemorrhages (Fig. 3). Therefore, the patient was concomitantly treated with bolus infusion of rFVIII. On day 2 of admission, his abdominal pain gradually improved, but the blood test showed mild progression of anemia (hemoglobin 10.0 g/dL).

Since a contrast-enhanced CT scan revealed no hematoma enlargement, conservative treatment with rFVIII was continued. He received a bolus infusion of rFVIII (25 IU/kg x 2/day) for 8 days, followed by single infusion (50 IU/kg/day) for 12 days. Echocardiography revealed that the hematoma gradually reduced in size spontaneously (Fig. 3). His knee extension and abdominal pain gradually improved. On day 20 of admission, rFVIII (50 IU/kg) was administered every other day, and the patient was discharged on day 28.

We assessed the hemostatic potential of this case. We could not analyze his blood sample upon admission because he was a primary contact of his parents (who had been diagnosed with COVID-19). After confirming negative results for COVID-19, Adimin11 and emicizumab concentration in his plasma were measured on day 2 of admission. Since the patient’s plasma contained residual exogenous FVIII:C, the samples were used after the addition of purified FVIII inhibitor IgG. The Adimin11 was 5.2, and the emicizumab concentration was 36 µg/mL, showing good efficacy of emicizumab treatment (Fig. 4). FVIII:C and Adimin11 during concomitant

![Fig. 2 Clinical course of Case 1 (with intracranial hemorrhage). We measured FVIII:C using a one-stage clotting assay with two anti-Emi monoclonal antibodies. The Adimin11 in the patient’s plasma on admission was also measured after the addition of purified FVIII inhibitor IgG to neutralize FVIII:C. The dosage of FVIII administration was 33 IU/kg on admission. Subsequently, continuous infusion of rFVIII concentrates was conducted. The patient required a 4–4.6 IU/kg/hr dose to maintain a FVIII:C of 50 IU/dL. We then measured Adimin11 using modified CWA and FVIII:C during continuous infusion. Nine days later, the patient was administered rFVIII at 66 IU/kg for 2 days and 33 IU/kg for 2 days. Adimin11 and FVIII:C were also measured just before FVIII administration. The gray bar represents the normal range (IQR: 6.9–7.7) of Adimin11 in 17 healthy individuals. Symbols used: closed circles, Adimin11 during the therapeutic period; open circles, FVIII:C during the therapeutic period; closed squares, Adimin11 on admission; FVIII:C, FVIII activity; rFVIII, recombinant FVIII; Adimin11, adjusted maximum coagulation velocity; CWA, clot waveform analysis.](image1)

![Fig. 3 Time course of changes in abdominal CT and ultrasound findings in Case 2. Abdominal CT findings showed left retroperitoneal and iliopsoas muscle hemorrhages on days 1 and 2. Abdominal ultrasound findings showed improvement in the retroperitoneal hemorrhage.](image2)
therapy were also measured. The trough FVIII:C level at 24 h after administration was maintained in the range of 20–30 IU/dL. The Adimin11 increased to 5.8–6.8, likely reflecting global coagulation potential > 40 IU/dL of equivalent FVIII:C [20]. As the therapeutic dose of FVIII was reduced along with the improvement in symptoms, FVIII:C and Adimin11 values were close to the baseline level. FVIII inhibitors were not detected.

**Discussion**

To date, there have been few case reports of traumatic extra-articular bleeding in emicizumab-treated PwHA. A recent case report [21] described the development of a hemophilic pseudo-tumor caused by constant damage from non-invasive positive-pressure ventilation in a 14-year-old boy receiving emicizumab prophylaxis. In this patient, emicizumab might not have been effective due to the low steady-state concentration (18 µg/mL). However, our patients experienced intracranial, iliopsoas, and retroperitoneal hemorrhages due to trauma, even though emicizumab prophylaxis showed good efficacy in both cases. We successfully treated them using the same dosage of rFVIII product as when emicizumab was not administered. To our knowledge, our report is the first to describe the management of severe traumatic bleeding such as intracranial, iliopsoas, and retroperitoneal hemorrhages in pediatric PwHA receiving emicizumab prophylaxis.

Intracranial hemorrhage was observed more frequently in younger children (especially those aged <2 years) without prophylaxis [3, 4], indicating a high risk of intracranial hemorrhage in pediatric PwHA. Powell et al. [22] demonstrated that spontaneous intracranial bleeding in severe PwHA occurs only when the FVIII:C is <2 IU/dL, primarily in children under the age of 4 years. Therefore, emicizumab prophylaxis could provide a sufficient hemostatic level to prevent spontaneous intracranial bleedings. Mason et al. [23] also suggested that emicizumab prophylaxis in infant PwHA reduced the risk of intracranial hemorrhage. However, our patient (Case 1) treated with emicizumab prophylaxis experienced a traumatic intracranial hemorrhage. One of the reasons may be that emicizumab does not have a suppressive efficacy of traumatic bleeding. In addition, hemophilia patients who have experienced intracranial hemorrhage have a higher risk of the recurrent bleeding [22]. Taken together, the higher level of FVIII:C than emicizumab could be required to prevent traumatic intracranial hemorrhage in PwHA.

Iliopsoas hemorrhage in PwHA is the most severe type of muscle hemorrhage [5]. Retroperitoneal hemorrhage in PwHA is also a serious hemorrhage that requires large amounts of FVIII products and blood transfusions [6–8]. According to previous reports of retroperitoneal hemorrhage in severe PwHA, acute anemia due to excessive blood loss was observed in all patients. They were treated with FVIII supplementation, bypassing agents, or FXIII products, while receiving packed red blood cells [6–8]. In contrast, no blood transfusions were required in our case because acute anemia was not observed, even though a massive retroperitoneal hemorrhage was detected. This could be due to the enhanced coagulation potential of emicizumab in Case 2.

We recently reported that CWA was useful for managing emicizumab-treated PwHA with FVIII inhibitors during the perioperative period [24]. CWA could also evaluate the coagulant potential in PwHA complicated with severe traumatic hemorrhages, treated concomitantly with emicizumab and high-dose bolus infusion of rFVIII or continuous infusion of rFVIII. CWA results showed that the coagulation function in emicizumab-treated PwHA without inhibitor was within normal values, even though they were treated with high-dose infusion of rFVIII or continuous infusion of rFVIII, supporting the safety of such concomitant therapy regimens. On the other hand, Santagostino et al. [25] reported that TGA in PwHA with inhibitors treated with rFVIIa and emicizumab appeared unlikely to be correlated with clinical conditions. In addition, TGA is time intensive.
for analyzing coagulation function [26], indicating that it may not be suitable for managing emergency cases. As for ROTEM assay, our earlier study demonstrated that the NATEM mode on ROTEM likely reflected near-physiological coagulation status and could assess global coagulation potentials in emicizumab-treated PwHA [27]. On the other hand, our modified CWA assay enabled to evaluate both emicizumab concentration in patients’ plasmas and global coagulation function [17]. Therefore, CWA could be a more appropriate tool for managing emicizumab-treated patients with severe traumatic hemorrhage.

In our case study, traumatic extra-articular bleeding was caused by trauma 3–4 days before. We recently demonstrated that the bleeding patterns in emicizumab-treated PwHA could be classified into three categories: (i) spontaneous bleeding, (ii) post-traumatic bleeding within 1–2 days, and (iii) delayed post-traumatic bleeding after 1–2 weeks [17]. Our cases also warn that care must be taken to avoid severe breakthrough bleeding caused by trauma several days before.

One limitation in this presentation was that we did not investigate using the other global coagulation assays (e.g., TGA and ROTEM). Nevertheless, we could follow the treatment plan and assessed the coagulation potential in emicizumab-treated pediatric PwHA with traumatic extra-articular bleeding using modified CWA. Utmost care must be taken about traumatic breakthrough bleeding in pediatric PwHA receiving emicizumab prophylaxis.

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Data availability statement The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

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