ACTH therapy for West syndrome with severe hemophilia A

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Abstract
Hemophilia A is an X-linked recessive disorder caused by factor VIII deficiency, which is an important factor in the coagulation system. Here, we describe a 1-year-old boy with hemophilia A who developed West syndrome (WS). Recombinant factor VIII was administered during adrenocorticotropic hormone (ACTH) therapy to prevent intracranial hemorrhage. Infusion of factor VIII at fixed intervals is useful for the safe administration of ACTH therapy for patients with WS with severe hemophilia A. A coagulation screening test should be performed before ACTH therapy.

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1. Introduction

West syndrome (WS) is the most common early-onset epileptic encephalopathy and is characterized by infantile spasms, hypsarrhythmia on electroencephalography (EEG), and developmental arrest or regression [1]. The etiology of WS is heterogeneous, including infections, perinatal events, and congenital genetic disorders [2]. Although adrenocorticotropic hormone (ACTH) is probably the most effective treatment for WS, serious adverse effects can occur [3].

Hemophilia A is a group of coagulation disorders that result from blood coagulation factor deficiency. Hemophilia A is the most common type of hemophilia and is an X-linked recessive disorder induced by factor VIII deficiency, but reports of WS with hemophilia A are rare [4]. Here, we describe a case of WS with severe hemophilia A.

2. Case report

The patient was a 1-year-old boy who was the second child of healthy unrelated parents. His uncle on his mother’s side suffered from severe hemophilia A and received factor VIII infusions at fixed intervals. The patient was born by uncomplicated, normal vaginal delivery at full term with a birth weight of 2405 g. At ages 4 and 7 months, he had recurrent episodes of seizure with sudden flexions of the upper and lower limbs 3–4 times a week. He was referred to our hospital at age 1 year with a chief complaint of daily seizures that occurred in clusters from 11 months. Physical and neurological examinations were normal with no dysmorphic features. Hemoglobin was 8.8 g/L, red blood cell (RBC) count was 426 × 10^12/L, and coagulation studies revealed normal prothrombin time (PT) and prolonged activated partial thromboplastin time (aPTT) of 67.3 s (reference range: 25.0–43.0). Coagulation factor assay revealed severe factor VIII deficiency (<1 IU/mL). He was diagnosed with severe hemophilia A. Interictal EEG showed very high-amplitude slow waves mixed with spikes, suggesting hypsarrhythmia. Brain magnetic resonance imaging (MRI) and computed tomography (CT) results were normal. Based on neuropsychomotor delay, EEG findings of hypsarrhythmia, and spasms, which occurred in clusters, a diagnosis of WS was formed.

Vitamin B6 was administered as the first treatment for WS but was not effective. Although he received oral valproic acid and zonisamide, spasms did not disappear. Finally, synthetic ACTH (0.0125 mg/kg/day) was administered intramuscularly daily for 2 weeks. Before ACTH therapy, factor VIII infusion test was performed to determine the dosage of the coagulation factor. Factor VIII levels were routinely measured, and an infusion of factor VIII was performed at fixed intervals to keep the trough level >2 IU/dL to prevent lethal hemorrhage. Inhibitor levels were also checked. While receiving ACTH, the previous medications of antiepileptic drugs were continued. Adrenocorticotropic hormone therapy achieved cessation of spasms after 7 days. Although brain CT showed cerebellar atrophy, intracranial hemorrhage was not observed.

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3. Discussion

This patient had WS with severe hemophilia A. Adrenocorticotropic hormone therapy was effective, and infusion of factor VIII at fixed intervals was useful for safe administration of ACTH therapy.

Our patient had WS with severe hemophilia A. The etiology of WS is heterogeneous, including genetic and acquired causes such as hypoxic–ischemic encephalopathy, tuberous sclerosis complex, chromosomal disorders, cerebral malformations, infections, metabolic disorders, intracranial hemorrhage (ICH), and stroke [2]. There are few reports of patients with hemophilia with nonsyndromic epilepsy. Only one case of hemophilia A complicated with WS was reported [4]. The patient showed no ICH by CT and MRI scans similar to our case.

Intracranial hemorrhage is a significant complication for children with hemophilia and occurs in approximately 5% of all untreated and severe cases [5]. Neonatal ICH can be a presenting feature of severe cases in about 3–4% [6]. Single remote symptomatic seizures often occur in perinatal and childhood ICH, and 13% of children with perinatal or childhood ICH developed epilepsy by 2 years of age [7]. Coagulopathy accounts for 15% of the etiologies of ICH. Although Ganesan and Kirkham suspected that a small ICH not detected by intracranial images might trigger seizures in a patient with hemophilia A complicated with WS [4], the underlying etiology of our case is unknown.

Adrenocorticotropic hormone therapy is a widely used and effective treatment for WS. Significant side effects of ACTH therapy include infection, hypertension, and cerebral atrophy with subsequent subdural hematoma [8]. Subdural hematoma results from tearing of the bridging veins due to acute cerebral atrophy. Cerebral atrophy was observed in all Japanese patients who were treated with ACTH, varying from minimal to massive [9]. Although it is generally accepted that the adverse effects of ACTH are dose-dependent, subdural hematoma may occur even during administration of low-dose ACTH therapy [8]. Close monitoring of adverse effects, especially subdural hematoma, is necessary. Therefore, prophylactic infusions of factor VIII were performed every other day to prevent subdural hematoma and other bleeding episodes. Our patient completed ACTH treatment without severe adverse effects. Then, infusion with the coagulation factor at fixed intervals might be required for the safe administration of ACTH therapy for patients with WS with coagulopathy.

The diagnosis of hemophilia in our case was based on the existence of family history. The reliability of clinical history might be low, and family history might not be helpful for patients with inherited coagulopathy resulting from spontaneous mutation or the variable expression of a coagulopathy [10]. Indeed, marked bruising and hematoma at the intramuscular injection site of ACTH may lead to the diagnosis of hemophilia A without family history [4]. Some children with bleeding disorders may be identified first during preoperative coagulation testing. Thus, coagulation screening prior to ACTH therapy should be routinely performed to prevent potentially fatal bleeding.

In conclusion, we report that an infusion of factor VIII at fixed intervals should be used for the safe administration of ACTH therapy for patients with WS with severe hemophilia A. Because the identification of pediatric patients at risk of hemorrhage before ACTH therapy might result in a change in management of treatment, coagulation screening tests should be performed prior to ACTH therapy.

Conflict of interest

The authors declare that there are no conflicts of interest.

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