Brief Communication

West syndrome associated with glycogen storage disease type 1b

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Abstract

A girl born at 41 weeks of gestation experienced a seizure involving the extremities 12 hours after birth. Hypoglycemia was observed, although various tests failed to identify the cause of hypoglycemia. Thereafter, her development and weight gain were normal, and no hypoglycemia was observed. At five months of age, atypical spasms occurred concomitant with hypoglycemia. The patient was diagnosed with glycogen storage disease type 1b based on genetic testing. Hypsarrhythmia on electroencephalography (EEG) revealed West syndrome. The hypoglycemia were treated by continuous nasogastric tube feeding and neutropenia by injection of granulocyte-colony stimulating factor (G-CSF). The spasms and hypsarrhythmia did not improve by administration of oral antiepileptic drugs including vigabatrin. However, the symptoms improved with 0.011 mg/kg adrenocorticotropic hormone (ACTH) and G-CSF therapy, with no apparent adverse effects. ACTH was a safe treatment for an immunocompromised patient.
Introduction

West syndrome (WS) is an infantile epileptic encephalopathy and is often drug resistant. Several conditions including metabolic disorders [1] can cause WS. Glycogen storage disease (GSD) is a metabolic disorder in which glycogen accumulates in tissues due to deficiencies in relevant enzymes or transporters of glycogen synthesis. GSD type 1b is caused by a deficiency in glucose-6-phosphate translocase due to a mutant G6PT gene [2]. Neutropenia is also a characteristic of GSD type 1b, with severity ranging from mild to severe. We encountered a case of WS with hypoglycemia and neutropenia caused by GSD type 1b. Herein, we report a case that was successfully treated with adrenocorticotropic hormone (ACTH) and granulocyte-colony stimulating factor (G-CSF) therapy, without adverse effects.

Case Report

The family of the infant described in this report provided informed consent for the publication of anonymized case details.

Past history

A female neonate was delivered at 41 weeks of gestation, weighing 2954 g at birth, with Apgar scores of 9 (1 min) and 10 (five min). There were no remarkable findings during pregnancy. There was no family history of significant diseases including metabolic and neurologic disorders. The neonate’s blood glucose level at 4 h after birth was 60 mg/dL. At 2 h after birth, however, a seizure in the right lower extremity was observed. The blood glucose level was 5 mg/dL at that time and recovered to 80 mg/dL after glucose infusion. From two to seven days, seizures did not occur but apnea was observed. A respirator was used until she was five days old. Laboratory investigations revealed no remarkable findings. Fluid-attenuation inversion recovery magnetic resonance imaging (MRI) of the head revealed high-intensity lesions in bilateral parietal lobes, as well as mild laryngomalacia. The cause of apnea was not fully understood at that time. The patient was discharged at one month and seven days of age, and no abnormal lesion of the head was observed on MRI. Involuntary extremity movements were observed at one month and 21 days of age. However, blood glucose level and electroencephalogram (EEG) were normal.

At three months of age, the patient was referred to the authors’ hospital. Although paroxysmal arm movement was observed by her parents, they did not disclose this to the physicians. The patient’s development appeared to be normal at this point. She was able to laugh, make bubbling sounds, maintain eye contact, and sit with arms supported but was unable to turn over.

Present medical condition and examinations

The patient was admitted for further evaluation at five months of age. On the day of admission, feeding was stopped for 3 h to prepare for sedation. Irritability was observed, and her blood glucose level was 5 mg/dL, which recovered to 46 mg/dL after glucose infusion. The patient’s height was 65.3 cm (+0.30 SD), body weight was 7300 g (+0.36 SD), body temperature was 36.7°C, heart rate was 100 beats/min, respiratory rate was 30 breaths/min, and blood pressure was 90/48 mmHg. The patient exhibited a doll-like faci-
al appearance, distended abdomen, hepato-
megal\(y\) (three fingers’ breadth beneath the
costal margin), and a reddened 2-cm papule
in the left inguinal area. No other rashes or
lymph node swellings were observed. The
patient was alert with normal cranial nerves
and isotonic muscle tone. There were no ab-
normal tendon reflexes, involuntary move-
ments, or cerebellar symptoms. Laboratory
investigations revealed neutropenia [white
blood cell count, 7800/\(\mu\)L and neutrophils
(absolute count, 234/\(\mu\)L)]. MRI of the head
was normal.

### Investigations and clinical course

GSD type 1b caused by mutation was sus-
pected because of hepatomegaly, neutropenia,
and hypoglycemia. Other disorders including
ACTH deficiency, infection, and immunode-
ficiency were excluded based on the test re-
results. \(G6PT\) (SLC37A4) gene sequencing re-
vealed a heterozygous mutation (c.322C\(\rightarrow\)T,
p.W118R and c.1108G\(\rightarrow\)T, p.G370*), con-
firming a diagnosis of GSD type 1b.

The clinical course is shown in Figure 1. Hypoglycemia was treated by GSD formula
feeding though a nasogastric tube. Cefazolin
140 mg/kg/day was administered for seven

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**Figure 1.** The clinical course of the patient.
The lowest daily blood glucose levels are shown. IV: intravenous infusion, CEZ: cefazolin, ST:
Sulfamethoxazole/trimethoprim, IVIG: intravenous immunoglobulin, VB\(_6\): vitamin B\(_6\), ZNS: zo-
nisamide, VPA: sodium valproate, VGB: vigabatrin
days to treat cellulitis. Neutropenia was treated by daily subcutaneous injection of G-CSF. Oral sulfamethoxazole (35 mg/kg/day)/ trimethoprim (7 mg/kg/day) was also administered. The patient did not develop additional signs of infectious diseases. Asynchronous flexor spasms of the neck and extremities were observed approximately 20 times a day from the first day of admission, but they did not occur in series. The interictal EEG is shown in Figure 2a. Multifocal and diffuse irregular spikes along with high voltage waves were frequently observed during sleep, similar to those found in hypsarrhythmia. These findings support the diagnosis of WS. Administration of oral antiepileptic drugs including vitamin B₆, zonisamide, sodium valproate (VPA), and vigabatrin did not improve the EEG profile (Figure 2b). The level and frequency of the seizures did not change. We administered intravenous γ-globulin (IVIG) at 200 mg/kg/day for 5 days during VPA treatment, and repeated after a week. However, there was no response.

In addition to daily injection of G-CSF, ACTH (0.011 mg/kg) was administered daily for 3 weeks. The frequency of spasms was reduced after 3 days of ACTH administration and seizures were altered after 14 days. Blood glucose and neutrophil levels were higher than those before treatment. The G-CSF administration was reduced to once eve-

Figure 2. Interictal electroencephalogram.
A: Hypsarrhythmia was observed before treatment. B: Hypsarrhythmia remains after vigabatrin treatment. C: A few irregular spikes and waves in the left central region are apparent after adrenocorticotropic hormone treatment.
For two days, but tube feeding was maintained. There were no symptoms of infection during the ACTH treatment and the dose was gradually reduced, while zonisamide (ZNS) was added. EEG during awake state showed small numbers of focal spikes and waves (Figure 2C). No spasms occurred during the two-year observation period. At the last follow-up, the patient was on maintenance dose of ZNS, and EEG showed no obvious worsening.

Discussion

Based on findings in this particular case, we propose that GSD type 1b may be a cause of symptomatic WS, and that ACTH treatment is effective for patients with neutropenia and is not associated with adverse effects.

To the best of our knowledge, there are no reports in the literature that describe an association between GSD and WS, although metabolic disorders can cause symptomatic WS. It is known that hypoglycemia is a cause of WS [1, 3-4]. In these cases, hypoglycemia was caused by hyperinsulinemia or brain injury confirmed by head magnetic resonance imaging during the neonatal period. Persistent hypoglycemia probably resulted in brain injury. Hershkovitz et al. [5] performed continuous glucose monitoring in a small number of patients with GSD type 1 and observed intervals of hypoglycemia (glucose levels < 50 mg/dL or 2.8 mmol/L) suggesting intermittent hypoglycemia in these patients. We believe that hypoglycemia in our patient was a direct cause of symptomatic WS.

We successfully used ACTH in an immunocompromised patient with WS undergoing G-CSF therapy. In our hospital, vitamin B₆ is the first line treatment for WS, and ACTH is used only when vitamin B₆ is ineffective. In this patient, we hesitated to use ACTH due to the adverse effects of immunosuppression, given that both bacterial and viral infections have been previously reported [6, 7]. Conventional anti-epileptic drugs were not effective in this case. Vigabatrin has recently been approved in Japan, and its efficacy is comparable with that of ACTH [8]. In our case, vigabatrin did not improve the EEG findings and the spasms. There was no loss of vision during treatment, which is an adverse effect of vigabatrin. ACTH was effective in altering the abnormal EEG findings, and the neutrophil count was maintained within target levels (>700/µL). Thus, ACTH can be safely used when immunocyte levels are stable. There were no symptoms of infection during treatment.

In conclusion, GSD type 1b may be a cause of symptomatic WS. In this case, ACTH was effective in an immunocompromised patient with WS, who was undergoing G-CSF therapy. Nevertheless, further studies investigating the long-term outcomes of these treatments are needed.

Conflicts of interest

The authors have no financial or personal relations that could pose a conflict of interest.

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