Case report

Hypofibrinogenemia caused by adrenocorticotropic hormone for infantile spasms: A case report

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Abstract

We report the case of a 7-month-old boy who developed hypofibrinogenemia (66.6 mg/dL; reference value, 170–405 mg/dL) during adrenocorticotropic hormone (ACTH) therapy for infantile spasms. Although the patient showed no clinical signs of a bleeding diathesis, we recommend that plasma fibrinogen levels should be monitored during ACTH therapy, which should be discontinued when fibrinogen levels fall below hemostatic levels (60.0 mg/dL) or when bleeding tendencies are recognized.

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1. Introduction

We have previously reported the cases of 4 infants who developed transient hypofibrinogenemia during combined therapy with valproic acid (VPA) and adrenocorticotropic hormone (ACTH) for infantile spasms [1]. In that report, we concluded that the hypofibrinogenemia may have been a side effect of VPA, which is known to cause hypofibrinogenemia; furthermore, there had been no published reports of hypofibrinogenemia caused by ACTH monotherapy. Here we report a recently encountered case of hypofibrinogenemia caused by ACTH monotherapy for idiopathic infantile spasms in a 7-month-old male child.

2. Case report

A 7-month-old boy was referred to our hospital with a chief complaint of infantile spasms since he was 5 months old. The patient was the first child born to healthy unrelated parents by spontaneous delivery after 41 weeks of an uneventful pregnancy. There was no significant family history. His parents, on noticing the spasms, sought treatment from his primary care doctor, who initially diagnosed the condition as normal infantile behavior. At the first visit to our hospital, his height (68.4 cm), weight (9.6 kg), and head circumference (45.2 cm) were normal. His psychomotor development was normal, with a developmental quotient of 112 as per the Enjoji Scale of Infant Analytical Development. Complete blood count, blood chemistry, blood coagulation, thyroid function, and urinalysis were normal. Electroencephalography revealed typical hypsarrhythmia. Computed tomography demonstrated a normal brain parenchymal structure without calcification. He
was diagnosed with idiopathic infantile spasms and was administered ACTH (synthetic ACTH-Z, 0.01 mg/kg/day every day for 2 weeks; Cortrosyn Z, Daiichi Pharmaceutical Corporation, Tokyo, Japan). His spasms ceased completely on day 5 of treatment, and the hypersarrhythmia resolved by day 8. However, his plasma fibrinogen levels gradually decreased over the treatment period (Table 1) and reached a level of 66.6 mg/dL (reference value, 170–405 mg/dL) on day 13 of treatment. ACTH therapy was thus discontinued, and his fibrinogen levels returned to the normal range after 4 days. The patient exhibited no bleeding diathesis during this period; furthermore, his liver function and brain magnetic resonance imaging (MRI) findings were normal.

3. Discussion

We encountered a case of hypofibrinogenemia caused by ACTH therapy for infantile spasms in a 7-month-old boy. The fibrinogen levels decreased to 66.6 mg/dL 13 days after the initiation of ACTH therapy; however, this level was not lower than that (60 mg/dL) typically required for hemostasis. A review of the relevant literature revealed 4 reports, including our own, on hypofibrinogenemia caused by the combined use of VPA and ACTH [1–4]; however, there was no report on hypofibrinogenemia caused by ACTH monotherapy for infantile spasms. Tokuda et al. [2] reported that plasma fibrinogen levels decreased significantly to 22–64 mg/dL in 3 patients with infantile spasms after ACTH was added to VPA at a dose of 0.03–0.04 mg/kg/day. According to Suemaru et al. [3], plasma fibrinogen levels decreased to 47–115 mg/dL in 7 patients with infantile spasms and 1 patient with Lennox–Gastaut syndrome when ACTH was administered at a daily dose of 0.10–0.25 mg/day (dose per kilogram body weight was not provided) concomitantly with VPA. Hirota-Kawadobora et al. [4] reported 2 patients with infantile spasms whose plasma fibrinogen levels decreased to 49–89 mg/dL. In our patient, we used 0.01 mg/kg/day of ACTH. Even though the dose was lower than that in the report by Tokuda et al. [2], the patient still developed hypofibrinogenemia.

Hirota-Kawadobora et al. [4] classified the causes of hypofibrinogenemia as follows: (1) decreased synthesis due to hepatic disease, (2) increased consumption due to massive hemorrhage or thrombosis, (3) side effects of L-asparaginase, (4) fibrinogen deficiency/dysfibrinogenemia, and (5) “unclassifiable” hypofibrinogenemia caused by VPA and ACTH. Our patient belonged to the unclassifiable category according to family history, previous medical history, serum biochemistry, and coagulation tests.

The side effects of VPA monotherapy include hypofibrinogenemia [5], which is also stated in the package inserts. Meanwhile, there have been no reports on hypofibrinogenemia caused by ACTH monotherapy. ACTH stimulates the secretion of adrenocortical hormones, and most therapeutic effects of ACTH are probably mediated by glucocorticoids. However, it also exerts direct effects on other organs, for example, it is considered to exert direct effects on the hepatocytes that promote fibrinogen synthesis [6]. Even with this data, the mechanism underlying hypofibrinogenemia caused by ACTH remains unknown.

The significant side effects of ACTH therapy include infection, hypertension, and cerebral atrophy with subsequent subdural hematoma [7]. Of these, subdural
hematoma results from the tearing of the bridging veins because of acute cerebral atrophy. There is a risk of increased hemorrhage volume in patients complicated by severe hypofibrinogenemia.

This case report indicates a high likelihood of hypofibrinogenemia after the use of ACTH for infantile spasms, suggesting that hypofibrinogenemia caused by ACTH therapy should be considered for inclusion in the diagnostic and therapeutic guidelines for infantile spasms [8]. In the event of ACTH-induced hypofibrinogenemia, the drug should be discontinued when plasma fibrinogen levels fall below the levels required for hemostasis. If hypofibrinogenemia leads to bleeding tendency, then immediate fibrinogen supplementation is necessary. Fibrinogen concentrate is far safer than fresh frozen plasma or cryoprecipitate. Although it is not approved in Japan for the treatment of acquired hypofibrinogenemia [9], fibrinogen concentrate is recommended as an off-label use. It may be used prophylactically, but specific plasma target level for the ACTH-treated patients with infantile spasms has not been established.

References