Acute Occlusion of the Ventriculoperitoneal Shunt Due to Factor XIII Deficiency-related Postoperative Hemorrhage: A Case Report

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Abstract

Coagulation factor XIII (F13) deficiency has been known to be a rare disease with estimated one per two million and one of the possible reasons of postoperative hemorrhage; however, it still remains unpenetrated to physicians. We report a case of acute ventriculoperitoneal (VP) shunt dysfunction due to delayed intraventricular hemorrhage, which could be because of F13 deficiency. The patient was a 48-year-old man with a history of post-meningitis hydrocephalus followed by VP shunt placement. He was found unconscious and transferred to our hospital. A brain CT scan demonstrated shunt malfunction, and he underwent emergency shunt revision. The postoperative course was uneventful except for unexpected neck bruises and continuous minor bleeding from the surgical wound. Three days after surgery, he suddenly became comatose and a CT scan revealed the recurrence of hydrocephalus with newly identified small volume of intraventricular hemorrhage. Emergency shunt revision was performed again. The shunt valve was filled with a hematoma and bloody cerebrospinal fluid was drained from the ventricle. Postoperative blood sample examination demonstrated no abnormal findings but a decreased level of F13 activity, which was thought to be a possible cause of postoperative hemorrhage and the shunt valve hematoma. F13 deficiency causes delayed intracranial hemorrhage 24–48 h after neurological surgery. It can only be diagnosed by checking F13 activity with suspicion. If diagnosed accurately beforehand, unexpected postoperative bleeding can be preventable with proper treatment, such as F13 concentrate and cryoprecipitate. The actual number of the patient with F13 deficiency may be more than estimated ever.

Keywords: factor XIII, factor XIII deficiency, ventriculoperitoneal shunt, shunt malfunction

Introduction

Coagulation factor XIII (F13) circulates in the blood and plays a role in cross-linking fibrin through the activation of thrombin. F13 deficiency is known to be a rare disease with estimated incidence of one per two million[1] and could be a possible cause of postoperative hemorrhage. This is classified into congenital and acquired subtypes. Both subtypes can cause postoperative hemorrhage.[2]

Congenital F13 deficiency is an autosomal recessive disorder characterized by bleeding, abnormal wound healing, and repeated miscarriage.[2,3] F13 deficiency is often first seen in postnatal umbilical cord hemorrhage.[1] Based on genotype, there are two types of F13 deficiency. The most common is F13-A subunit deficiency, caused by mutations in the F13A1 gene (chromosome 6, p24–25). F13-B subunit deficiency is caused by underlying mutations in the F13B gene (chromosome 1, q32–32.1) and accounts for <5% of cases. Both types result in the absence of F13 catalytic activity in plasma.[3]
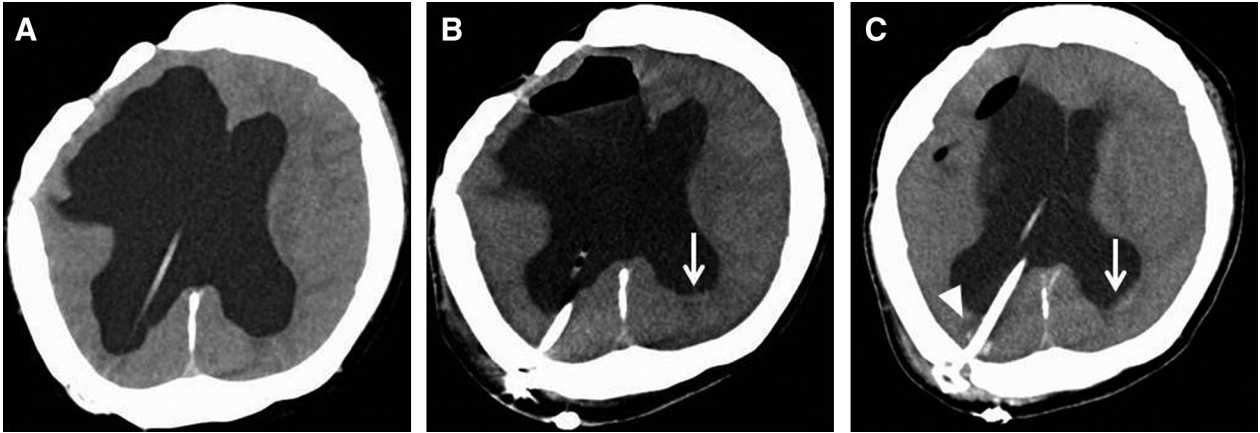
Fig. 1 Preoperative brain CT showing hydrocephalus (A), brain CT on postoperative day 1 after first shunt revision surgery showing improvement of hydrocephalus (B), and brain CT on postoperative day 3 showing progressed ventriculomegaly with intraventricular hemorrhage and parenchymal pericatheter hemorrhage (C) (the white arrows show intraventricular hemorrhage and the white arrowhead shows parenchymal pericatheter hemorrhage).

Acquired F13 deficiency is also known to be attributed to over-consumption of F13 due to major surgery, various underlying diseases, or production failure, in which F13 decline is generally mild and rarely noticed even after bleeding. Since there is no prolongation of the coagulation time or abnormalities in platelets, it is considered to be a disease that is difficult to diagnose using normal preoperative screening blood tests alone or even notice if postoperative bleeding occurs.[1]

Here, we report a case of shunt malfunction 3 days after shunt reconstruction due to a fresh hematoma tightly packing the shunt valve. Postoperative examination demonstrated F13 deficiency. We discuss the relationship between F13 deficiency, known as a rare disease that has not yet shown penetrance, and shunt malfunction attributed to valve hematoma.

Case Report

The patient was a 48-year-old man who was performed a right ventriculoperitoneal (VP) shunt for post-meningitis hydrocephalus at 7 months of age. Two months after the operation, bilateral subdural hematomas were found and removed by bilateral craniotomies. Multiple VP shunt reconstructions were subsequently performed. The last shunt reconstruction surgery was performed when he was 11 years old. He had intellectual disabilities and his intellect was around 12 years old. He had residual left hemiplegia and was regularly taken to the outpatient clinic with a 4-point cane. There was no other medical history or family history to be noted.

He visited our hospital due to a day-long disturbance of consciousness. He was comatous and a brain CT scan showed progressive ventricular enlargement and disappearance of the sulcus (Fig. 1A), which suggested shunt malfunction. Chest abdominal CT showed that the abdominal tube had come out of the abdominal cavity. Shunt reconstruction was performed urgently on the same day.

First operative findings

The shunt valve was a differential pressure type. Since the ventricular catheter tightly adhered to surroundings, its removal was abandoned. A new ventricular tube was inserted from the brain surface after ventricular puncture. Clear, non-bloody cerebrospinal fluid (CSF) was drained from the catheter. CODMAN CERTAS Plus (Integra LifeSciences, Princeton, NJ, USA) was used as the valve and the operation was completed in a standard manner without any difficulty of hemostasis. The amount of bleeding was too small to measure.

Postoperative course

On the next day, he regained consciousness and had no new neurological deficit other than the original left hemiplegia. Postoperative course was uneventful except for continuous minor bleedings from the head and abdominal wounds. Subcutaneous hemorrhagic bruises were also observed along the shunt pathway in the right neck and chest (Fig. 2). Brain CT on postoperative day 1 showed a decreased ventricular size and a tiny volume of ventricular hematoma that formed a slight niveau in the ventricles (Fig. 1B). On postoperative day 3, he suddenly experienced bradycardia, apnea, and loss of consciousness. The shunt valve was immediately punctured, and a pressure measurement was taken; the intracranial pressure was over 40 cm H_2O. The bloody CSF was then quickly drained. Immediately after

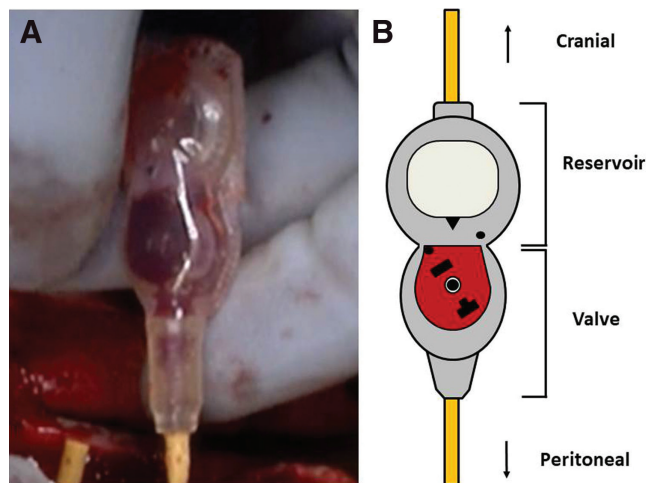**Fig. 2 Subcutaneous hemorrhagic bruises along the shunt pathway.**

Fig. 3 Intraoperative picture (A) and schematic representation (B) of shunt valve obstructed by hematoma (hematoma in the programmable portion of the valve is colored red).

this maneuver, his respiratory status, heart rate, and consciousness level improved slightly. The subsequent CT scan demonstrated progressed ventriculomegaly with intraventricular hemorrhage and subcutaneous hematoma around the shunt valve. The parenchymal pericatheter hemorrhage was also noticed (Fig. 1C); consequently, emergency shunt reconstruction was performed. On the blood test, the platelet count was 165000/μl, activated partial thromboplastin time (aPTT) was 30.8 s, prothrombin time-international normalized ratio (PT-INR) was 1.08, and fibrinogen was 454 mg/dl.

Second operative findings

The programmable portion of the valve was filled with a hematoma (Fig. 3), which was considered to cause the acute shunt occlusion, while there was no hematoma in reservoir portion of the valve, which was filled with slightly bloody CSF. Outflow of CSF from the ventricular catheter was good, while the intraventricular CSF was bloody, and the pressure was 50 cmH$_2$O. Since the presence of the bloody CSF may have blocked the shunt again, CSF was washed repeatedly with ARTCEREB (Otsuka Pharmaceutical, Tokyo, Japan) (1 l was used) using a newly inserted ventricular catheter till it became almost colorless. The peritoneal catheter was patent and CODMAN HAKIM Programmable Valve (Integra LifeSciences) was placed.

After the second surgery, his consciousness gradually improved. Hemorrhage from the wound was also noted at this time but could be managed conservatively. The patient was referred to the hematology department for further investigation of this hemorrhagic event, which revealed that F13 activity had decreased to 49% (normal value: 70%–140%) on postoperative day 3 by quantitative assay (ammonia release assay). There was a recovery to 60% on the 12th day and 84% on the 31st day; therefore, the

patient was diagnosed with F13 deficiency. F13 inhibitor and autoantibody were not evaluated. Coagulation factor V, VIII, and von Willebrand factor were not evaluated, while other coagulation-related factors such as aPTT, PT-INR, protein C activity, protein S activity, antithrombin III, and lupus anticoagulant were all in normal range. Since then, he has had good progress and has recovered. He was discharged on the 23rd day after surgery.

Discussion

To the best of our knowledge, this is the first report that F13 deficiency caused acute VP shunt malfunction due to a valve hematoma from delayed intraventricular hemorrhage. F13 deficiency is known to be a very rare disease and could be a plausible cause of postoperative hemorrhage; however, it has a low clinical penetrance and is unfamiliar to many clinicians.

Persistent bleeding after minor injuries or surgery and formation of hematomas after minor trauma in infancy, intracranial hemorrhage is a characteristic feature of congenital F13 deficiency, with an incidence of 23% and high mortality.[4] Acquired F13 deficiency has immune and non-immune causes, which include overconsumption of F13 due to surgery, infection, embolism, and impaired production due to liver failure, leukemia, drug-induced, and other factors.[2] Therefore, taking a proper patient history, including family history and physical exam is the first step to diagnose F13 deficiency.[1,5] After that, F13 deficiency can be confirmed via laboratory evaluation. The laboratory evaluations mainly involve clot solubility test, FXIII activity assay, FXIII antigen

assay, inhibitor assay, and molecular diagnosis as well as detection of causative mutation in F13-A or F13-B genes.[1,5–7] Quantitative assay, if available, is first-line screening test recommended.[5] The patient had no history of persistent bleeding, liver failure, malignancy, or autoimmune disease and no family history of bleeding tendency. He underwent multiple shunt operations for hydrocephalus after meningitis in his childhood; however, this is the first time to be noticed that the postoperative hemorrhage attributing to shunt malfunction was caused from F13 deficiency. If he was suffering from a congenital F13 deficiency, he may have had more postoperative bleeding complications. Moreover, quantitative assay revealed his F13 activity had decreased to 49% on postoperative day 3. Kohler et al. reported that increased consumption or decreased synthesis results in reduced F13 activity levels typically ranging from 20% to 70%, whereas patients with inherited F13 deficiency reduced F13 activity to less than 3%.[7] These support that he had an acquired F13 deficiency. He had a past history of postoperative hemorrhage with unknown cause 2 months after the operation. It is less likely that F13 deficiency caused this hemorrhage because F13 deficiency-related hemorrhage usually occurs 24–48 h after stabilization of thrombi. F13 inhibitor and autoantibody should have been examined for a more detailed evaluation.

F13 plays a role in fibrin cross-linking and contributes to the stabilization of thrombi. It has been reported that F13 deficiency prevents fibrin from being stabilized and that the fibrinolytic system dissolves the thrombus once formed.[8] In these patients, clots may form normally but begin to break down abnormally 24–48 h later because of weak cross-linking of fibrin, leading to subsequent episodes of bleeding.[1] This patient developed acute shunt malfunction due to a shunt valve hematoma 3 days after the initial surgery. Since no additional force was applied to remove the ventricular catheter, which adhered to the surrounding tissue in the first operation, the removal of the ventricular catheter was abandoned. Therefore, it is unlikely to be the cause of the intraventricular hemorrhage. Shunt surgery itself can contribute to the intracerebral hemorrhage, as previously reported,[9] but the amount of intraventricular hemorrhage commonly thought to be too small to make hematoma in the shunt valve. Although hemostasis was confirmed before closing the wound, postoperative bleeding, such as wound oozing and subcutaneous hemorrhagic bruises along the shunt pathway, was confirmed. Brain CT on postoperative day 3 showed subcutaneous hematoma around the shunt valve and pericatheter hemorrhage. Considering time course, F13 deficiency caused these delayed hemorrhages, which dropped into the ventricles, leading to valve occlusion. The programmable portion of the valve was filled with a hematoma, while there was no hematoma in the reservoir portion of the valve. The diameter of programmable portion is narrower than that of reservoir portion. It is considered that stagnation of bloody CSF occurred in programmable portion resulted in forming a hematoma. Brydon et al. reported that shunt valves were adversely affected by blood suspensions in dilutions from 0.25% to 1%.[10] The valves were sometimes partly blocked and were at other times incompetent.[10] We have to keep in mind that in patients with F13 deficiency, even a small amount of postoperative bleeding can cause shunt obstruction and can be a fatal complication.

Intracranial hemorrhage is known to be more frequent with F13 deficiency than with other coagulation factor deficiencies.[11] Gerlach et al.[12] reported that the F13 level was significantly lower in the group exhibiting bleeding after intracranial surgery compared to that in the non-bleeding group. Besides, those patients with a postoperative F13 <60% have 6.4-fold risk of developing a postoperative hematoma. They also reported that all patients with F13 deficiency (8 patients out of 1264 who underwent intracranial operations) had a major postoperative hemorrhage in other paper.[4] The authors reported that six patients underwent tumor resection and developed postoperative subgaleal, epidural, subdural, and tumor-resection-cavity hematoma, which required evacuation. One patient underwent chronic subdural hematoma evacuation and developed postoperative subdural hematoma. The other patient underwent VP shunt and developed subcutaneous hematoma but she did not need reoperation.[4] We have to know that F13 deficiency may cause several kinds of delayed hemorrhage and it can lead to a poor outcome. The point is that F13 deficiency can only be diagnosed by detecting the decreased F13 activity level and the diagnosis of F13 deficiency only can start with the suspicion of this disease. Although the number of the patients with F13 deficiency is known to be very small, we suspect that there may be more patients than that of estimated.

Treatment of F13 deficiency can be divided into two types depending on whether it is immune-mediated or not.[6] Immune-mediated F13 deficiency requires hemostatic therapy, such as administration of high dose (50–150 U/kg) F13 concentrates or F13-containing blood products,[13] or requires immunosuppressive therapies using corticosteroids, cyclophosphamide, rituximab, cyclosporine, and intravenous immunoglobulin.[6] Non-immune-mediated F13 deficiency can be treated with F13 replacement including highly purified plasma-derived F13 concentrate such as Fibrogammine (CSL Behring, King of Prussia, PA, USA) and

recombinant F13-A2 concentrate.[14] Cryoprecipitate and frozen plasma are candidates of alternative.[15] The goal of factor replacement is to achieve adequate hemostasis, which may require a level greater than 10%. In the surgical setting, a F13 target of 50% has been reported in case series involving perioperative patients with congenital or acquired F13 deficiency.[16,17] Fortunately, in this case, the patient's consciousness and general condition improved after shunt reconstruction. His F13 level spontaneously increased within a month, which is consistent with the report by Chuliber et al.[18] describing that 74% (20 out of 27) of patients with nonimmune-acquired F13 deficiency normalized F13 in 15 days or more after diagnosis. If there is persistent bleeding, persistent decrease in F13, or if F13 deficiency is known or expected preoperatively, administering F13 concentrate should be considered.

We report a case of VP shunt malfunction attributed to F13 deficiency-related valve hematoma. In patients with F13 deficiency, even a small amount of postoperative bleeding can cause shunt obstruction and can be a fatal complication. When unexpected persistent bleeding at the surgical wound or unexpected subcutaneous hemorrhagic bruises are noticed, one should proactively consider F13 deficiency and investigate it as long as other coagulation factors remain within their normal ranges. If F13 deficiency is diagnosed before postoperative hemorrhage occurs, it may be possible to prevent unexpected postoperative bleeding with proper treatment as a fail-safe strategy. Although the F13 deficiency is known to be a rare disease, there may be more patients than estimated ever.

Conflicts of Interest Disclosure

All the authors have no conflicts of interest.

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