Management of hydrocephalus in infants with severe hemophilia A: report of 2 cases

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The authors report on the clinical course of two infants with severe hemophilia A (HA) and concomitant progressive hydrocephalus that required management with a ventriculoperitoneal shunt. The first child, with known HA, presented with a spontaneous intracranial hemorrhage and acquired hydrocephalus. He underwent cerebrospinal fluid diversion with a temporary external ventricular drain, followed by placement of a ventriculoperitoneal shunt. The second child had hydrocephalus secondary to a Dandy-Walker malformation and was diagnosed with severe HA during preoperative evaluation. He underwent placement of a ventriculoperitoneal shunt after progression of the hydrocephalus. The authors also review the treatment of hydrocephalus in patients with HA and describe the perioperative protocols used in their two cases. Treatment of hydrocephalus in infants with HA requires unique perioperative management to avoid complications.

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KEYWORDS hemophilia; hydrocephalus; ventriculoperitoneal shunt; Dandy-Walker; intracranial hemorrhage

PEDIATRIC hydrocephalus is a surgically correctable condition, but infants with primary coagulopathies require unique management. Hemophilia A (HA) is a disorder caused by a deficiency of factor VIII (FVIII), and severe HA is defined by plasma FVIII activity less than 1%.⁶ Children with HA are at an increased risk for intracranial hemorrhage (ICH).²⁶ If intraventricular hemorrhage occurs, it can lead to hydrocephalus.^{9,21,23}

Case Reports

Case 1

Presentation

A boy was born at term via cesarean section given concerns about macrocephaly. His family history was positive for HA, and neonatal testing confirmed a diagnosis of severe HA. Subsequent mutation analysis revealed an intron 22 inversion. He was treated on demand with an extended half-life (EHL) recombinant FVIII (rFVIII) product. He received his first dose of rFVIII at 8 weeks of life as part of a study protocol.

At 14 weeks, he experienced 4 days of vomiting and increased irritability. He presented to the emergency department, where he experienced a seizure characterized by left eye deviation. He received 50 IU/kg standard half-

life (SHL) rFVIII and then underwent head CT, which demonstrated a 4-cm hematoma involving the left lateral ventricle with heterogeneous attenuation. He was placed on a continuous infusion of SHL rFVIII targeted to levels of 80%–120% and was admitted to the pediatric intensive care unit.

An MRI study again demonstrated the hematoma and showed moderate supratentorial ventricular enlargement and an incidental suprasellar cyst (Fig. 1). An MRA was negative for a secondary cause of bleeding.

Inpatient Course

The rFVIII infusion was adjusted with daily labs to maintain a level of 80%–120%. He also received 14 days of oral prednisolone (including a scheduled wean) in an attempt to prevent anti-FVIII inhibitor formation. Serial imaging showed no increase in ventricle size and a persistent left lateral ventricle blood clot. He had intermittent seizures treated with levetiracetam. On admission day 7, an external ventricular drain (EVD) was placed due to increasing ventriculomegaly and signs of increased intracranial pressure (ICP) including a bulging anterior fontanelle on examination. After 10 days of cerebrospinal fluid drainage, the EVD was clamped; however, the patient continued to have dilated ventricles (on serial head ultrasonography

ABBREVIATIONS DWM = Dandy-Walker malformation; EHL = extended half-life; EVD = external ventricular drain; FVIII = factor VIII; HA = hemophilia A; ICH = intracranial hemorrhage; ICP = intracranial pressure; rFVIII = recombinant FVIII; SDH = subdural hematoma; SHL = standard half-life; VP = ventriculoperitoneal.

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FIG. 1. Axial T2-weighted (left) and sagittal FIESTA (right) MR images obtained at presentation, showing intraventricular hemorrhage, moderate ventricular enlargement, and an incidental suprasellar cyst.

studies) and signs of elevated ICP (new-onset bradycardia), so ventriculoperitoneal (VP) shunt placement was recommended.

Prior to surgery, he received stress-dose steroids. His FVIII levels were monitored daily throughout the perioperative period, and the continuous infusion was adjusted to levels of 100%–120%. The VP shunt was placed in the right lateral ventricle via a frontal approach. There was minimal blood loss and no complications.

On postoperative day zero, ultrasonography showed decompressed ventricles without signs of hemorrhage. Uninterrupted rFVIII infusion continued for 7 days with a maintenance target FVIII level of 80%–100%. On postoperative day 7, the patient was transitioned to bolus SHL rFVIII infusions to achieve FVIII troughs $\geq 50\%$ for 7 additional days. Bolus dosing was continued for 4 more weeks with a targeted trough of $\geq 25\%$. He had no additional bleeding during this interval. At 6 weeks postoperatively, he was transitioned to once daily dosing with a targeted trough of $> 1\%$. His trough was $< 1\%$ despite daily dosing with an SHL product, so he was transitioned to EHL rFVIII and successfully maintained troughs on daily dosing.

At the 6-month postoperative evaluation, he was following developmental milestones, displaying good visual tracking, and had no neurological deficit. Imaging showed decompression of the ventricles and a new Chiari malformation type 1 (Fig. 2). The latter was most likely a re-

FIG. 2. Limited T2-weighted MR images obtained at 6 months postoperatively, showing an incidentally found Chiari malformation type 1 with cerebellar tonsillar descent to 9.8 mm below the foramen magnum.

FIG. 3. Preoperative sagittal T2-weighted MR image showing hypoplasia of the cerebellar hemispheres and vermis, a retrocerebellar cyst communicating with the fourth ventricle, and an enlarged posterior fossa. Also observed were hypoplasia of the brainstem and mild ventriculomegaly of the lateral and third ventricles.

flection of his increased ICP during the attempted EVD clamp trial. He had no evidence of inhibitors and was subsequently transitioned to dosing every 36 hours to maintain trough levels $> 1\%$.

Case 2

Presentation

An abnormal prenatal ultrasonography study at 28 weeks led to the diagnosis of Dandy-Walker malformation (DWM) in this infant. Labor was induced at 37 weeks for failure to thrive, and the infant was delivered via cesarean section for failure to progress. At birth, the boy's head circumference was at the 30th percentile. Neonatal MRI showed structural anomalies consistent with a DWM and mild ventriculomegaly (Fig. 3).

He was developmentally normal at 2 months. Genetic workup was positive for 16p13.11 microduplication.

At 14 weeks of life, he displayed right-sided preference with torticollis. His head circumference had increased to the 99th percentile, and imaging demonstrated an increase in the volume of the lateral and third ventricles and split cranial suture lines. Neurosurgery was consulted, and the clinical evaluation was negative for signs or symptoms of increased ICP. Due to the significant increase in ventricle size and the crossing of two curves on his head circumference growth chart, a VP shunt was recommended.

One day after a laboratory blood draw, the patient presented to the emergency department with arm swelling in the antecubital fossa. Laboratory studies demonstrated an elevated activated partial thromboplastin time, and a diagnosis of severe HA was confirmed with FVIII $< 1\%$. His family history was negative for HA. Surgery was post-

TABLE 1. Perioperative rFVIII management for VP shunt in infants with HA

Course	Case 1, ICH	Case 2, DWM
Initial treatment	ICH: 50 IU/kg SHL bolus, followed by CI to target 80%–120%; levels checked every 12 hrs	Arm hematoma: 50-IU/kg EHL bolus; followed by 50-IU/kg every 12 hrs for 48 hrs; then 50-IU/kg every 24 hrs for 48 hrs; & then 50-IU/kg every 48 hrs for 72 hrs
Inpatient maintenance	Oral prednisolone for 14 days; CI target 80%–120%	Prophylactic: bolus of 50 IU/kg twice weekly
Preop	Bolus 50 IU/kg; CI at 5 IU/kg/hr, target 100%–120%	Bolus of 50 IU/kg; CI at 5 IU/kg/hr, target 80%–120%
Intraop	CI target 80%–120%	CI target 80%–120%
Postop	POD 0–7: CI w/ target 80%–100%; POD 7–14: bolus infusion every 12 hrs, trough target $\geq$ 50%; POD 15–42: bolus infusion every 24 hrs	POD 0–4: CI for 4 days, target 80%–120%; POD 5–14: bolus infusion every 12 hrs, trough target $\geq$ 50%; POD 15–42: bolus infusion every 24–48 hrs, trough target $>$ 25%
Discharge	POD 8	POD 5

CI = continuous infusion; POD = postoperative day.

poned for management of the arm hematoma given concerns about impending compartment syndrome. Treatment was initiated with an EHL rFVIII concentrate. The hemorrhage resolved after an initial 50-IU/kg bolus, followed by a 50-IU/kg bolus every 12 hours for 48 hours, then every day for 48 hours, and then every other day for 72 hours. Upon resolution of the hematoma, the patient was transitioned to a prophylactic regimen of 50 IU/kg twice weekly. No anti-FVIII inhibitors developed during these initial exposures to rFVIII. After 9 exposure days to rFVIII, the boy was reassessed in the neurosurgery clinic, and because of an increased head circumference and increasing lethargy, the hemophilia and neurosurgery teams collaborated on a management plan for VP shunt placement (Table 1).

Inpatient Course

On the morning of surgery, he received a bolus of 50 IU/kg rFVIII and a continuous infusion was initiated at 5 IU/kg/hr. Levels were obtained to maintain a goal of 80%–120%. A VP shunt was placed in the right lateral ventricle via a right frontal approach. There was minimal blood loss and no complications.

Postoperatively, he continued to receive the continuous infusion of rFVIII for 4 days with a target of 80%–120%. Head CT confirmed placement of the VP shunt but also demonstrated small bilateral subdural hematomas (SDHs; Fig. 4), without midline shift or mass effect. Hemoglobin and hematocrit levels were stable. Follow-up ultrasound studies revealed resolution of these hematomas prior to discharge on postoperative day 5. The boy was weaned to dosing every 12 hours with FVIII troughs $\geq$ 50% through postoperative day 14. He was then transitioned to daily dosing to keep troughs $>$ 25% to complete 6 weeks of therapy. At 2 months' follow-up, he was doing well and attaining expected developmental milestones. No FVIII inhibitors developed.

Discussion

Management of hydrocephalus in infants with severe HA requires unique considerations by the neurosurgeon and hematologist. These case reports offer examples of two different perioperative management scenarios and illustrate the importance of multidisciplinary collaboration.

Hematological Management

A feared complication of HA treatment is the development of anti-FVIII inhibitors, which occur in 22%–30% of patients and can render FVIII treatment ineffective.^{14,18} Known risk factors for anti-FVIII inhibitor development include the type of FVIII mutation, patient race, and family history. Potential risk factors include FVIII therapy in the setting of infection, inflammation, or surgery; type of rFVIII concentrate; and intensity of rFVIII treatment.¹⁴

Primary prophylaxis with FVIII replacement reduces the risk of ICH and is recommended early in life.² Previously untreated patients are at increased risk of developing anti-FVIII inhibitors, but low-dose primary prophylactic rFVIII decreases this risk.^{3,14} The patient in case 1 required immediate high-dose rFVIII to treat an acute bleed; therefore, the hematology team recommended a trial of immune suppression with steroids for the theoretical benefit of reducing inflammation and preventing inhibitor development. Anticipation of a nonemergent VP shunt surgery provided time for perioperative care of the coagulopathy. Surgery was delayed for the DWM patient, so the initiation of low-dose rFVIII was possible. The World Federation of Hemophilia provides separate recommendations for the management of FVIII levels in an acute hemorrhage and for surgery.³¹ In both of our cases, the recommendations were adapted to the scenario (Table 1) and were influenced by close communication between the surgeon and the hematologist. Also, the use of an EHL product in case 2 allowed for earlier transition to bolus dosing.

FIG. 4. Coronal CT scans obtained preoperatively (left) and on postoperative day 1 (right). Note the bilateral subdural bleeds of 5 and 4 mm at the vertex.

Neurosurgical Management

Intracranial hematomas can occur as a complication of shunt procedures, and most bleeds are SDHs,^{15,24} which can range in size. Therapeutic options include evacuation of the SDH, but asymptomatic bleeds are often conservatively monitored on serial imaging.¹ Despite adequate rFVIII levels, our patient with DWM developed small, bilateral SDHs after VP shunting, which were followed with ultrasound studies to resolution. Preventing an interruption to the rFVIII infusion was paramount for avoiding excess bleeding, and care teams were instructed to avoid any line obstructions. Nonsteroidal anti-inflammatory drugs and intramuscular medicines were avoided. Factor VIII assays were sent immediately postoperatively and were obtained daily.

Intracranial hemorrhages in the pediatric HA population are often spontaneous⁹ and more frequent in the first 2 years of life.^{5,19} Management of ICH requires early recognition and immediate FVIII replacement. For a presumed ICH, FVIII levels should be immediately raised to initial levels of 80%–100% for 1–7 days, followed by troughs of 50% for 8–14 days.³¹ Surgical intervention is performed in 33%–39% of cases.^{9,32,39} In one retrospective study of 66 children with a primary coagulopathy and ICH, 22 underwent surgery, which consisted of craniotomy and evacuation in 16 cases and insertion of a VP shunt or drain in 6 cases.⁹ However, these studies did not describe the management of FVIII levels for children who develop hydrocephalus and require surgery. Our report offers specific examples of perioperative FVIII management leading to successful surgery.

Reports of hydrocephalus in patients with HA, as seen in our patients, are scarce.^{9,29,37} A VP shunt is indicated if temporizing measures fail to control the ICP and if hydrocephalus persists.¹³ In certain cases, an alternative to shunt placement is endoscopic third ventriculostomy with or without choroid plexus cauterization, which has been reported in the treatment of DWM-associated hydrocephalus.^{34,35} The benefit of this procedure is to avoid future surgery related to shunt hardware infection or malfunction. The surgeon must weigh the potential benefits against the potential complications, which include uncontrolled bleeding, injury to vascular structures, and a variable failure rate based on different factors.⁷ Endoscopic third ventriculostomy has been reported in HA patients but has failed and required a shunt or its outcome was unknown.^{8,20} With the appropriate protocol (Table 1), VP shunting can be performed with minimal blood loss.

Dandy-Walker malformation accounts for approximately 1% of developmental obstructive hydrocephalus in infants,²⁷ and obstructive hydrocephalus in the setting of hemophilia is also rare. A literature review revealed two cases of obstructive hydrocephalus in adults with HA attributed to arachnoid cysts; one cyst was located in the middle fossa and required shunting¹³ and the other was located in the suprasellar region.²² Other cases of cysts in HA have been reported but either the patients did not develop hydrocephalus or the cyst was considered an incidental finding.⁴

The unusual concomitant finding of HA and DWM warrants a brief discussion. The *F8C* gene responsible

for HA is cytogenetically located at Xq28. Also located at Xq28 is the gene *LCAMI*,¹¹ which is implicated in the most common genetic cause of congenital hydrocephalus, the X-linked L1 syndrome.^{33,36} L1 syndrome also includes central nervous system malformations that are similar to DWM, such as cerebellar hypoplasia, small brainstem, and hypogenesis of the medullary pyramids.^{16,36} Our case provides a clinical example of an association between HA and DWM. Multiple case series have reported a male predominance in DWM (ratio 1.4–2.0),^{25,30,35} which may suggest an X-linked process.^{10,38} Mutations in X-located genes, such as *LCAMI* and *OPHN1*, can cause cerebellar dysgenesis and DWM.^{17,28} The mutation status of such X-linked genes in our patient is unknown.

Conclusions

In summary, our cases demonstrate that with a multidisciplinary approach, our treatment of hydrocephalus with a VP shunt was safe in the management of infants with HA. Although each case requires individualization based on severity of hemophilia and type of FVIII concentrate utilized, our treatment examples may provide value to other neurosurgeons and hematologists facing similar problems.

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Author Contributions

Conception and design: Drapeau, Bergin. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Bergin. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Drapeau. Study supervision: Drapeau.

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