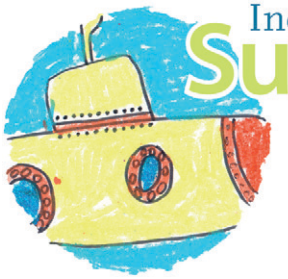

Index of Suspicion

1 Listlessness in a 4-month-old Girl

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CASE PRESENTATION

A 4-month-old girl presents with 1 day of listlessness and poor feeding. She is exclusively breastfed and was born at term. There are no reports of trauma. She is fully vaccinated for her age, received vitamin K after birth, and has been healthy to date.

On physical examination, the girl's temperature is 37.8°C (100°F), respiratory rate is 26 breaths/min, heart rate is 133 beats/min, blood pressure is 111/63 mm Hg, and oxygen saturation is 100% in room air. Her weight is 6.8 kg (45th percentile), length is 63 cm (55th percentile), and head circumference is 41 cm (50th percentile). She is pale and lethargic, with a distended abdomen, bruising of her chest, and a full but soft anterior fontanelle. Her eyes open in response to touch, and her pupils are symmetrically 3 mm in diameter and reactive to light. She does not withdraw to painful stimuli. The edge of her liver is palpable 4 cm below the right costal margin. Cardiac rhythm is regular, with a 2/6 soft systolic ejection murmur at the left sternal border, and she has mild tachycardia. Her lungs are clear on auscultation.

Laboratory testing reveals a hemoglobin of 4.1 g/dL (41 g/L), hematocrit of 13% (0.13), white blood cell count of 14,300/μL (14.3×10^9/L), and platelet count of $125\times10^3/\mu$L (125×10^9/L). Serum bilirubin measures 3.5 mg/dL (59.9 μmol/L), and the direct fraction is 2.2 mg/dL (37.6 μmol/L), with alanine aminotransferase of 1408 U/L (23.5 μkat/L) and aspartate aminotransferase of 1880 U/L (31.4 μkat/L). Analysis of her urine yields unremarkable results. Head computed tomography (CT) scan shows bilateral subdural hemorrhages of both acute and chronic appearance.

Interval development of right pupil dilation is noted upon admission to the intensive care unit, and a repeat head CT scan confirms new midline shift with uncal herniation due to expansion of the right subdural hemorrhage. After immediate craniectomy and clot evacuation, she is stabilized with multiple fresh frozen plasma and packed red blood cells transfusions, but severe anemia and coagulopathy persist. Her prothrombin and partial thromboplastin times are 90.6 seconds and 37.3 seconds, respectively, and all vitamin K-dependent clotting factors (II, VII, IX, and X) are low, while fibrinogen, factor V, and factor VIII are normal. Hemolytic anemia with pan-positive complement and immunoglobulin (Ig)G antibodies is noted on direct Coombs testing. After receiving a single dose of intravenous vitamin K, her coagulopathy corrects, but her anemia and cholestasis persist. The diagnosis is revealed after further evaluation.

EDITORS NOTE

We invite readers to contribute case presentations and discussions. Please use the Submit and Track My Manuscript link on the Pediatrics in Review homepage: http://pedsinreview.aappublications.org.

AUTHOR DISCLOSURE Drs Murray and Rister have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

CASE DISCUSSION

Needle biopsy of the liver showed marked giant cell change and cholestasis as well as formation of numerous pseudoacini causing distortion of the overall hepatic architecture, consistent with a diagnosis of giant cell hepatitis (GCH). Warm direct Coombs-positive autoimmune hemolytic anemia (AHA) was noted on further hematologic evaluation. Initial disease remission was achieved with the combination of intravenous immune globulin and high-dose intravenous corticosteroids. She was weaned successfully from the corticosteroids after starting on azathioprine. The departments of gastroenterology and hematology have followed her as an outpatient and monitored an uncomplicated initial recovery.

The Condition

Multiple pediatric case reports have described the combination of GCH and AHA (GCH-AHA). GCH is the fusion of injured hepatocytes and subsequent transformation into giant cells on histopathologic analysis, and it results in impaired hepatic function and cholestasis. Affected tissue samples have stained positive for classic complement proteins. Accordingly, although the cause of the hepatocyte injury remains unknown, it is believed to be initiated by the combination of underlying genetic susceptibility and B-cell autoimmunity. Case reports have implicated inherited diseases such as maternal blood group incompatibilities and congenital hemosiderosis as well as metabolic and infectious causes as potential triggers for induction of autoimmunity. Production of the hepatic autoantibodies that are classically found in autoimmune hepatitis is believed to be driven by inadequate or ineffective regulatory T cells, and testing for these yields negative results in GCH.

Direct Coombs-positive hemolytic anemia, which is the result of IgG autoantibodies binding to red cell surface membranes and triggering activation of the complement system with subsequent destruction of red cells, is a consistent finding in patients with GCH-AHA. This association lends further support to the theory that B-cell autoimmunity underlies the combined disorder.

Vitamin K deficiency in the context of neonatal cholestasis and exclusive breastfeeding has also been described in the pediatric literature. Associated deficiencies of vitamins A, D, E, and K, the fat-soluble vitamins, have suggested fat malabsorption as the presumptive link. Vitamin K levels in human milk are low, which further increases the risk in exclusively breastfed infants. Subdural hemorrhages have been reported previously as a presenting finding in this framework.

This case highlights the unique pathology with an all too common presentation. This infant had severe anemia due to AHA, cholestasis due to GCH, and vitamin K deficiency acquired from the combination of cholestasis and breastfeeding. When this presented as multiple subdural hemorrhages, the leading diagnostic consideration was nonaccidental trauma. A month-long diagnostic assessment with evaluation by multiple subspecialists and an extensive literature review was required to affirm the true cause of the patient's underlying bleeding disorder.

Management and Prognosis

Immunosuppressive therapies are the mainstays of treatment in GCH-AHA. Consistent success has been shown with corticosteroids, intravenous immune globulin, cyclophosphamide, and azathioprine. Recent literature has documented excellent clinical responses with rituximab and alemtuzumab, both of which are monoclonal antibodies that exert their effects via anti-B-cell activity. Initial improvement while receiving immunosuppressive therapy followed by frequent relapses of liver disease is typical of the clinical course in GCH-AHA. A significant number of patients eventually need liver transplants, and GCH frequently reoccurs in transplanted livers.

Lessons for the Clinician:

- GCH-AHA is a rare combination of diseases that presents with infantile cholestasis and Coombs-positive hemolytic anemia.
- The mechanism of GCH-AHA is unknown but is believed to be driven by B-cell autoimmunity.
- Cholestasis in combination with exclusive breastfeeding can result in late vitamin K-dependent bleeding, which can present with spontaneous intracranial hemorrhage.
- Inflicted trauma should remain high in the differential diagnostic consideration in any otherwise healthy patient with an intracranial hemorrhage and no reported history of trauma, but this case serves as a reminder that careful evaluation for causes other than child abuse is imperative.

Note: This case is based on a poster presentation by Dr Murray at the Pediatric Hospital Medicine Conference, Lake Buena Vista, Florida, Poster Session: B, Presentation Date: Sunday, July 27, 2014, Poster Number: 49.

References for this article are at http://pedsinreview.aappublications.org/content/36/7/311.full.

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