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Case Report

Bleeding diathesis due to vitamin K deficiency in an infant with cystic fibrosis

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ABSTRACT

With the wide implementation of newborn screening for Cystic Fibrosis, infants are being diagnosed in the presymptomatic phase of the disease. Nutritional deficiencies (hypoalbuminemia) and fat soluble vitamins A, D and E deficiencies, due to pancreatic insufficiency and malabsorption, have been reported in the past at the time of diagnosis.[1,2] Rarely, infants with CF present with severe bleeding disorder, secondary to vitamin K deficiency, in the first months of life.[3] To our knowledge, this is the first case report illustrating bleeding diathesis in a one month old infant with CF. He was diagnosed by newborn screening and presented with a gastrointestinal bleeding due to vitamin K deficient coagulopathy.

1. Introduction

With the development and implementation of the newborn screening (NBS) for Cystic Fibrosis (CF) it has become possible to identify children with CF, within the first 1–2 months of life, mostly in the presymptomatic phase of the disease.[1] Nutritional deficiencies (hypoalbuminemia) and fat soluble vitamins A, D and E deficiencies, due to pancreatic insufficiency and malabsorption, have been reported in the past at the time of diagnosis in some infants.[1,2] Rarely, infants with CF present with severe bleeding disorder, secondary to vitamin K deficiency, in the first months of life.[3] Vitamin K deficiency has been reported in older children with cystic fibrosis not receiving routine vitamin K supplementation.[4] Deficiency of vitamin K in children with CF may be due to variety of reasons, including inadequate dietary intake, maldigestion, and fat malabsorption, decreased intestinal synthesis of vitamin K following diarrheal disease or antibiotic administration.[4]

This report describes an infant with newly diagnosed CF who developed bleeding diathesis. He presented with hematemesis and blood in the stools at 4 weeks of age. Vitamin K deficient bleeding diathesis was confirmed with laboratory testing and symptoms resolved after vitamin K administration. This case is of interest because of the unique presentation and a potential for life-threatening complications associated with fat soluble vitamin deficiencies in young infants with CF if left untreated. It also illustrates the important role of the newborn screening program for early diagnosis of CF and timely intervention with appropriate therapy.

2. Case report

TF is a 4 week old Caucasian male infant diagnosed with CF through NBS. He had two mutations identified; R117H and G551D. He was born at full term, had routine care, including vitamin K prophylaxis at birth. At his initial clinic visit, on Day of Life (DOL) #24, he was noted to be "gassy and colicky" with yellow-green, foul smelling stools, 10 times a day. Weight gain was appropriate. Physical exam was unremarkable, except for a full but nontender abdomen, without organomegaly or palpable masses. Routine CF care was prescribed, including the use of nebulized bronchodilator, pancreatic enzymes and fat soluble vitamins supplementation. On DOL #29 his parents noted a streak of bright red blood in his stool, which was attributed to an anal fissure. On the same day he had emesis with brown streaks. Additional history suggested gastroesophageal reflux with frequent spitting up and fussiness after feeding. He was otherwise feeding well, with decreased stool frequency and improved gas symptoms. The brown streaks in the emesis were attributed to mucosal irritation from GE reflux and ranitidine was initiated. At a follow up visit on the next day, he continued to show good weight gain. There was no recurrence of the hematemesis. Occasional red-brown streaks were still noted in the stool. Fat soluble vitamins supplementation was just initiated on the day of the visit. Stool hemeoccult test was positive. He was referred for blood work.

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Table 1
Coagulation studies before and after administration of subcutaneous vitamin K.

	At presentation	7.5 h post vitamin K	Normal range
PT	>100 s	11.7 s	9.5–11.7 s
aPTT	86.1 s	23 s	23–32 s

Coagulopathy with markedly prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) was evident (Table 1). In addition, a complete blood count, comprehensive metabolic panel, and vitamin A level were all within appropriate limits. Alpha tocopherol was found to be below the normal range 2.6 (3.8–18.4 mg/l). A cranial ultrasound was performed which showed no hemorrhage. Vitamin K deficiency was diagnosed and the infant received 1 mg subcutaneous injection of vitamin K. Next laboratory evaluation, 7.5 h later, showed complete correction of his coagulopathy (Table 1).

Further evidence that the coagulopathy was due to a vitamin K deficiency was suggested by the levels of vitamin K dependent clotting factors at the time of presentation. Factor VII and Factor X, had an activity of less than 5% (normal range of 50–150%). Factor V, a non-vitamin K dependent clotting factor had an activity of 91% (normal range 50–150%). He was discharged home on daily ADEK vitamins and oral vitamin K supplementation three times a week. He had no further evidence of bleeding in the next few months. Repeat PT and PTT continued to be within normal limits.

3. Discussion

CF is the most common genetic disorder in Caucasians in the United States, with incidence of 1 in 3500.[5] The median age of clinical diagnosis on the basis of signs and symptoms other than meconium ileus is 14.5 months (interquartile range IQR: 4.2–65.0 months), compared with 0.2 month (IQR: 0–0.9 month) for meconium ileus and 0.5 month (IQR: 0–0.9 month) for newborn screening.[6] Diagnosis on the basis of symptoms among infants is associated with a >2-fold greater risk of medical complications before diagnosis than diagnosis resulting from NBS.[6] In 2004 newborn screening for CF was strongly recommended by both the CF foundation and the CDC.[7] That was followed by the majority of the states in the US, implementing the addition of CF NBS to their NBS panel. By the year 2010 all states are expected to provide CF NBS to their infants. Michigan started NBS in 2007.

In the era of standard parenteral (intramuscular) vitamin K prophylaxis at birth, vitamin K deficient bleeding and in particular late vitamin K deficient bleeding (VKDB), between 2 and 12 weeks of age is rare.[8] It was recommended in an American Academy of Pediatric Policy Statement that a single parental dose of 0.5–1 mg (intramuscularly) most effectively prevent late VKDB in infants.[8] Coagulopathy in infancy is a rare presentation of CF with a few recent cases described in the English literature. CF infants 2–3.5 months of age with manifestation of intracranial hemorrhage[3,9] and bruising and hematomas [10,11] have been described. We report on an infant with newly diagnosed CF through NBS, presenting with severe bleeding diathesis, manifesting as gastrointestinal bleeding. PT and aPTT were significantly elevated and vitamin K dependent clotting factors were significantly low, while the other clotting factors were not affected, suggesting vitamin K deficient etiology. To our knowledge, this is the youngest CF patient reported, presenting with severe bleeding diathesis, due to vitamin K deficiency. In this patient, routine intramuscular vitamin K administration at birth failed to prevent vitamin K deficient bleeding diathesis. The Vitamin K deficiency could be secondary to either insufficient intake, especially with the patient exclusively being breast fed, or due to malabsorption, given symptoms of pancreatic insufficiency (PI). However, pancreatic supplementation was started at time of diagnosis with expected improvement in PI.

Vitamin K deficiency was identified as virtually universal in older patients with CF and PI, prophylactic administration of vitamin K was recommended in this population.[12] The introduction of the fat-soluble vitamin combination was speculated by the authors to significantly decrease the prevalence of vitamin K deficiency.[12] The question remains as to how common fat soluble vitamin deficiencies are in the infant CF population identified by the newborn screen program and whether early supplementation would be warranted. A study by Sokol et al. in 1991 was performed to prospectively analyze the fat soluble vitamin deficiencies in newborns with CF identified by newborn screen. These children were receiving pancreatic enzyme supplementation as well as an infant multivitamin. It was found that none of these infants had vitamin K deficiency, based on negative PIVKA (proteins in vitamin K absence) test.[1] In 2002, the Consensus Report on Nutrition for Pediatric Patients with Cystic Fibrosis,[13] recommended daily supplementation with Vitamin K at a dose of 0.3–0.5 mg in addition to the daily age appropriate dose of multivitamins. In addition, the consensus states that fat soluble vitamin levels in patients diagnosed by newborn screening, do not need to be checked at the time of diagnosis.

CF care givers need to be aware that severe coagulopathy could happen in early infancy. The use of newborn screening to identify the diagnosis helps establish early close monitoring and initiation of appropriate therapies. Our case report emphasizes the necessity of screening for vitamin K deficiency by measuring PT and aPTT, as a surrogate[13] as soon as the diagnosis is established. We think this should be done especially in breast fed infants, regardless if the infants received parenteral vitamin K at birth. It also demonstrates the need for prompt recognition of symptoms of pancreatic insufficiency and initiation of supplemental fat-soluble vitamins and pancreatic enzymes especially in breast fed infants.

Conflict of interest statement

The authors have no conflict of interest.

References

1. Sokol RJ, Reardon MC, Accurso FJ, et al. Fat-soluble vitamins in infants identified by cystic fibrosis newborn screening. *Pediatr Pulmonol Suppl* 1991;**7**:52–5.
2. Feranchak AP, Sontag MK, Wagener JS, Hammond KB, Accurso FJ, Sokol RJ. Prospective, long-term study of fat-soluble vitamin status in children with cystic fibrosis identified by newborn screen. *J Pediatr* 1999 Nov;**135**(5):601–10.
3. Mérelle ME, Griffioen RW, Dankert-Roelse JE. Cystic fibrosis presenting with intracerebral haemorrhage. *Lancet* 2001 Dec 8;**358**(9297):1960.
4. Conway SP, Wolfe SP, Brownlee KG, et al. Vitamin K status among children with cystic fibrosis and its relationship to bone mineral density and bone turnover. *Pediatrics* 2005 May;**115**(5):1325–31.
5. Cystic Fibrosis Foundation – 2007 Patient registry report.
6. Accurso FJ, Sontag MK, Wagener JS. Complications associated with symptomatic diagnosis in infants with cystic fibrosis. *J Pediatr* 2005 Sep;**147**(3 Suppl):S37–41.
7. Grosse SD, Boyle CA, Botkin JR, et al. CDC. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Recomm Rep* 2004 Oct 15;**53**(RR-13):1–36.
8. American Academy of Pediatrics Committee on Fetus and Newborn. Controversies concerning vitamin K and the newborn. American Academy of Pediatrics Committee on fetus and newborn. *Pediatrics* 2003 Jul;**112**(1 Pt 1):191–2.
9. Hamid B, Khan A. Cerebral hemorrhage as the initial manifestation of cystic fibrosis. *J Child Neurol* 2007 Jan;**22**(1):114–5.
10. McPhail GL. Coagulation disorder as a presentation of cystic fibrosis. *J Emerg Med*; 2008 Mar 31 [Epub ahead of print].
11. Verghese T, Beverley D. Vitamin K deficient bleeding in cystic fibrosis. *Arch Dis Child* 2003 Jun;**88**(6):553.
12. Wilson DC, Rashid M, Durie PR, et al. Treatment of vitamin K deficiency in cystic fibrosis: effectiveness of a daily fat-soluble vitamin combination. *J Pediatr* 2001 Jun;**138**(6):851–5.
13. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2002 Sep;**35**(3):246–59.