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Profound hypocalcemia in an infant with jaundice

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Abstract

Although fat soluble vitamin deficiencies are common in cholestasis, it is unusual for their sequelae to be present at time of diagnosis. We report a case of symptomatic hypocalcemia at time of diagnosis of biliary atresia in a 10-week infant. Calcium repletion and subsequent vitamin and mineral supplementation was challenging in this case and required a multi-specialty approach. This case highlights the need for further research in oral water-soluble or parenteral fat soluble vitamin supplementation to better serve this patient population. In addition, we highlight the need to be aggressive in identifying and addressing the sequelae of fat soluble vitamin deficiencies such as hypocalcemia and coagulopathy.

Keywords

biliary atresia; fat soluble vitamins; cholestasis

Introduction

Fat soluble vitamin (FSV) deficiencies in infants with biliary atresia (BA) have frequently been reported in the literature and the pathophysiology is well understood. Diminished bile flow in BA leads to decreased intestinal bile acid secretion and thus, decreased absorption of fat and FSV [1-3]. Management of FSV deficiencies can be challenging in infants with cholestasis. The profound hypocalcemia secondary to vitamin D deficiency in our patient, with associated ECG changes, required prompt identification and correction, particularly to prevent cardiac arrhythmia.

Case Report

A previously healthy 10 week male infant presented with scleral icterus, with direct bilirubin of 10mg/dL (ref <1.2mg/dL). Additional routine admission labs revealed profound hypocalcemia with a serum calcium of 6.6mg/dL (ref 9 – 11mg/dL) and ionized calcium 0.83mmol/l (ref 0.95 – 1.5mmol/l), hyperphosphatemia with serum phosphate of 9mg/dL (ref 4 – 6.5mg/dL) and mildly abnormal coagulation profile (PT 14.7 sec [ref 12.8 – 15.5 sec], INR 0.91 [ref 0.92 – 1.17], PTT 43.1 [ref 24.5 – 34.6]).

Initial liver biochemistry tests showed Total Protein 6.5g/dL, Albumin 4.3g/dL, Alkaline Phosphatase (ALP) 1274 (ref 150-420U/L), Alanine Aminotransferase (ALT) 147 (ref 13-45 U/L), Aspartate Aminotransferase (AST) 164 (ref 9-80U/L), Gamma Glutamyl Transferase (GGT) 608 (ref 8-90U/L) [4].

ECG showed prolonged QTc (495ms) (ref ≤450ms). The infant was placed on continuous cardiac monitoring and initiated on intravenous and oral calcium supplementation. FSV deficiencies were found on hospital day 2, with 25-OH-vitamin D <4 ng/mL (ref 30-100ng/mL) and vitamin K1 0.13 ng/mL (ref 0.28-1.78 ng/ml). These were corrected with oral ergocalciferol and subcutaneous vitamin K injections.

After ultrasound and HIDA scan raised suspicion for BA, intraoperative cholangiogram confirmed the diagnosis. Liver biopsy was compatible with BA, with diffuse bile duct proliferation, bridging fibrosis, cholestasis, periportal inflammation and bile plugging. The patient successfully underwent Kasai hepatoportoenterostomy (HPE).

Both the endocrinology and cardiology teams were involved in the management of hypocalcemia in this infant. Several doses of IV calcium gluconate supplementation were required to normalize the infant's serum calcium level and correct the prolonged QTc on ECG. Figure 1 shows the trend of ionized calcium levels from diagnosis to discharge. Notably, the calcium levels fluctuated significantly despite correction and supplementation during the admission. At time of discharge, oral supplementation was continued with calcium carbonate (100mg QID), fat soluble vitamins (A, D, E and K) (0.5ml daily), and ergocalciferol (4000IU/day).

Discussion

Sequelae of FSV deficiencies in cholestasis are not as frequently reported in literature, particularly prior to or at time of diagnosis of cholestasis.

Clark et al in 1992 reported 2 cases of term infants who presented with symptomatic hypocalcemia and laboratory evidence of coagulopathy. In both cases, direct hyperbilirubinemia and elevated liver enzymes were identified serendipitously on routine admission tests and not suspected clinically. Multiple FSV deficiencies were later found, thought to be secondary to cholestasis. In both cases, the cause of cholestatic liver disease was not specifically established, however, BA was ruled out in both infants [5]. Another report by Ibdah et al in 1999 identified symptomatic hypocalcemia in an infant with cholestasis and long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency [6].

Intracranial hemorrhage associated with vitamin K-deficiency bleeding is a described complication in BA. A recent retrospective review identified intracranial hemorrhage in 7.95% of patients with BA [7]. A case series also from Japan identified intracranial hemorrhage in 15 cases [8]. There have also been individual case reports in recent years describing this complication [9, 10].

DeRusso et al, in 2003, reported 3 cases of infants with BA who sustained long bone fractures several months after hepatoportoenterostomy. Child abuse was suspected in all 3 cases and before investigation revealed significant osteopenia, thought likely secondary to vitamin D deficiency. Only one infant had biochemical evidence of hypocalcemia and hypovitaminosis D; serum chemistries were not drawn on the infants. The infant with hypocalcemia developed these complications despite oral vitamin D supplementation [11].

Our patient's vitamin D deficiency was difficult to correct, especially in the context of newly diagnosed BA and need for surgical intervention. This is a challenge echoed in the literature. Jensen et al in 2015 reported their experiences of oral vitamin D repletion in 4 cases of cholestasis. They suggested

that standard high dose repletion regimens used in children without cholestasis were not sufficient in their patient group, perhaps owing to decreased intraluminal bile acid secretion leading to poor absorption of enterally administered supplements [12]. A 2012 study of 90 infants with BA, performed by the Childhood Liver Disease Research and Education Network (ChiLDREN), assessed the biochemical progression of FSV deficiencies in children with BA who were being orally supplemented with fat soluble vitamins (A, D, E and K). Even after HPE, the prevalence of FSV deficiency was 100%, 79%, 50%, and 46%, respectively, for vitamins A, D, E, and K. This was especially important in patients with persistent cholestasis, evidenced by serum total bilirubin over 2mg/dL [13]. Shen et al in 2012 studied 23 patients with cholestasis and found high prevalence of FSV deficiencies despite conventional oral supplementation [3].Many of these groups cite parenteral FSV supplementation as a possible alternative. However, there is a need for randomized controlled trials in this area and the need for frequent hospital visits and painful injections are potential challenges [3,13].

With the high prevalence of FSV deficiencies in cholestatic infants, it is surprising that symptoms of downstream effects are not more widely reported in literature. This may be a result of timely diagnosis of BA, leading to early HPE and initiation of FSV supplementation. The patient in this report had a late presentation. The importance of early diagnosis of BA is widely accepted and there are universal guidelines in the work up of neonatal cholestasis [14]. Several strategies exist for early detection, including the stool color card used in Japan and more recently, the validated 'PoopMD' application [15,16]. Unfortunately, as in our case, some infants are diagnosed late (over 60 days of life) and thus may be prone to developing complications. Checking for biochemical evidence of FSV deficiencies and their sequelae in all cases of BA is paramount. This is especially critical in patients presenting late.

Figure

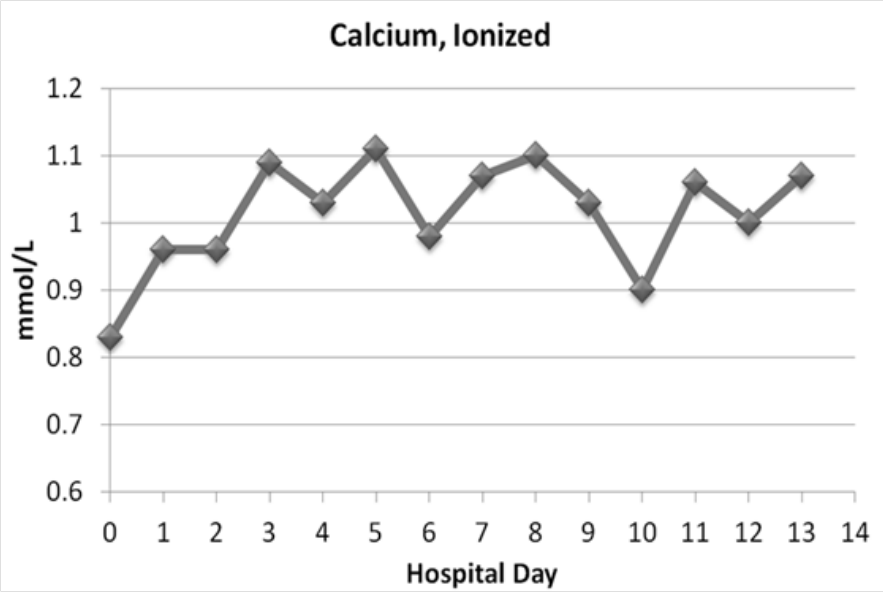

Figure 1: showing the trend of ionized calcium levels from diagnosis to discharge.

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