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Intracranial hemorrhage as a rare complication of cholestasis: A case report

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ABSTRACT

Cholestasis characterized by impaired bile secretion and flow, can lead to significant health risks in children, particularly due to its association with vitamin K deficiency. Infants with cholestasis are at increased risk for coagulopathies, manifesting as severe bleeding events, including intracranial hemorrhage (ICH). Despite vitamin K supplementation, the prevalence of deficiency remains high among affected children. This case report discusses the manifestation, diagnosis, and management of an infant with cholestasis with intracranial hemorrhage as a rare complication, emphasizing the importance of early detection and vitamin K supplementation to prevent severe neurological complications.

Keywords: Cholestasis, jaundice, intracranial hemorrhage, coagulopathies, infant

INTRODUCTION

Cholestasis refers to the stagnation or significant decrease in the secretion and flow of bile. The condition may arise from a functional impairment in the hepatocytes responsible for bile secretion and/or from an obstruction at any point along the bile excretory pathway. Cholestatic jaundice is categorized into intrahepatic or extrahepatic cholestasis, based on the degree of obstruction to bile flow.[1] Children with cholestatic liver disease have a heightened risk of secondary vitamin K deficiency due to issues with fat malabsorption and insufficient dietary intake. Consequently, infants experiencing cholestasis are especially at risk for coagulopathies, which can present as severe bleeding complications, such as intracranial hemorrhage (ICH).[2]

The actual prevalence of vitamin K deficiency in cholestatic liver disease remains unclear, leading to ongoing debates about the necessity of routine supplementation. Vitamin K

deficiency is commonly observed in children suffering from mild-to-moderate cholestatic liver disease, despite the administration of vitamin K supplements. The relationship between vitamin K deficiency and the extent of cholestasis, as well as the severity of liver disease in pediatric populations, is noteworthy.[3] Ensuring sufficient vitamin K levels in children with cholestatic liver disease is essential for promoting proper coagulation and potentially aiding in brain development. Vitamin K deficiency poses a significant risk for children with cholestatic liver disease, potentially resulting in severe hemorrhage that can lead to disability or fatal outcomes.[2]

Intracranial hemorrhage represents a rare yet significant complication in neonates experiencing cholestasis. The lack of vitamin K-dependent clotting factors—specifically factors II, VII, IX, and X—significantly contributes to the occurrence of hemorrhagic episodes, as these infants frequently exhibit coagulopathy.[3] Additionally, liver dysfunction linked to cholestasis may result in decreased production of coagulation factors, which can further increase the risk of bleeding.[4]

Timely identification and action are essential for enhancing results, as postponing the diagnosis of ICH can lead to significant neurological complications or fatality. This case report details the presentation, diagnosis, and management of an infant experiencing cholestasis complicated by intracranial hemorrhage, emphasizing the critical need for early recognition and suitable vitamin K supplementation.

CASE REPORT

A 3-month-old baby boy came to the emergency department of a tertiary hospital with a chief complaint of bloody stools four days ago. This occurred on average four times per day. Two days before admission, the patient had 2 episodes of seizures, the left hand twitched, and both eyes glanced up. The seizure lasted less than 1 minute and then stopped on its own. After the seizure, the patient cried weakly.

Previously, the patient was also presented with jaundice at the age of 5 days old and the stools started to turn pale one month later (Figure 1). Based on his medical history, the patient had 2 times 24 hours of phototherapy and blood transfusion. The patient was referred from the district hospital with a diagnosis of anemia gravis and suspected biliary atresia. He has pale-colored stools but this week his stools are dark blackish (Figure 2).

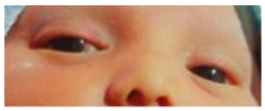

Fig. 1 CLINICAL MANIFESTATION OF JAUNDICE IN THE PATIENT.

Fig. 2 BLOODY STOOL OF THE PATIENT.

The patient was the first child, born spontaneously and born at term. At birth, the patient cried immediately, had reddish skin, moderately active movements, no cyanosis, and no jaundice. Birth weight was 3175 g and birth length was 49 cm. The patient received exclusive breastfeeding (0-1 month) and formula milk (1 month - current). Immunization status that has been obtained is Hepatitis B, BCG, and oral polio vaccine (OPV)[1]. Currently, the patient can only tilt to the right and left slightly, not yet able to lift the head.

The patient's general condition appeared weak and pale, compos mentis. The patient's anthropometric status showed a body weight of 3.6 kg, body length of 54 cm, head circumference of 38 cm, and abdominal circumference of 40 cm. Vital signs showed pulse 118 x/min, regular, respiratory frequency 24 x/min, adequate breaths, axillary temperature 36.7^{0}C, with oxygen saturation 99% free air. Physical examination showed slightly anemic conjunctiva, sclera icterus, no cyanosis, no dyspnea, round isochor pupils, positive direct light reflex, and positive indirect light reflex. Abdominal examination revealed hepatomegaly (5 x 4 x 2.5 cm), splenomegaly (S1H1). The skin of the body and extremities appeared jaundiced.

Laboratory examination showed hemoglobin levels of 10 g/dL, white blood cell level 10.15 x103/µL, platelet levels 480 x103/µL, and C-Reactive Protein 0.20 mg/dL. Peripheral blood smear showed anemia normochromic normocytic anisopoikilocytosis. Leukocytes with

atypical lymphocytes and immature granulocytes (+), and thrombocytosis. Another laboratory examination showed an increase in liver function levels (aspartate aminotransferase (AST) 160 U/L, alanine aminotransferase (ALT) 150 U/L, total bilirubin 10 mg/dL, direct bilirubin 6.4 mg/dL, albumin 2.6 g/dL, Alkaline Phosphatase (ALP) 295 U/L, gamma-glutamyl transpeptidase (GGT) 588 U/L, activated partial thromboplastin time (APPT) 52.3 sec, partial thromboplastin time (PPT) 44.1 sec) and HBsAg was non-reactive. TORCH laboratory examination showed Reactive Toxoplasma IgG (18.3 IU/ml), Reactive Rubella IgG (71.10 IU/ml), Reactive CMV IgG (117.8 AU/ml), and Reactive CMV IgM (4.46 Index).

A Head CT scan with contrast showed a hyperdense lesion with blood density (62 HU) measuring +/- 2.3 x 2.7 x 2.1 cm (volume +/- 3.2 cc) in the cortical-subcortical of the left parietal lobe accompanied by perifocal edema around it that presses and narrows the left lateral ventricle causing a midline shift of +/- 0.45 cm to the right side. There was a hyperdense lesion with blood density (90 HU) with a maximum thickness of +/- 0.88 cm in the subdural space of the left temporoparietooccipital region and left tentorium. There was a hyperdense lesion with blood density (62 HU) that filled the left temporooccipital subarachnoid space, Sulci effacement was accompanied by loss of white matter and gray matter differentiation with a large hypodense area in the right and left front temporoparietooccipital lobes (dominant subcortical) which cause cerebellar density to appear higher (pseudo hyperdense) than cerebrum (white cerebellum sign). On contrast administration, no lesions showing abnormal contrast enhancement were seen, and the ventricular system and cisterna outside the lesion appeared normal. Pons and cerebellum were normal. No abnormal calcifications were seen, no abnormalities were seen in the right and left orbits, mastoids, and paranasal sinuses, and calvaria was normal. There was intracranial hemorrhage (ICH) in the cortical-subcortical of the left parietal lobe (volume +/- 3.2 ccs) accompanied by perifocal edema around it that pressed and narrowed the left lateral ventricle causing a midline shift of +/- 0.45 cm to the right side, subdural hemorrhage (SDH) in the subdural space of the left temporoparietooccipital region with a maximum thickness of +/- 0.88 cm and in the left tentorium cerebelli with a maximum thickness of +/- 0.4 cm, and left temporooccipital subarachnoid hemorrhage (SAH) - suspicion of Hypoxic Ischemic Encephalopathy.

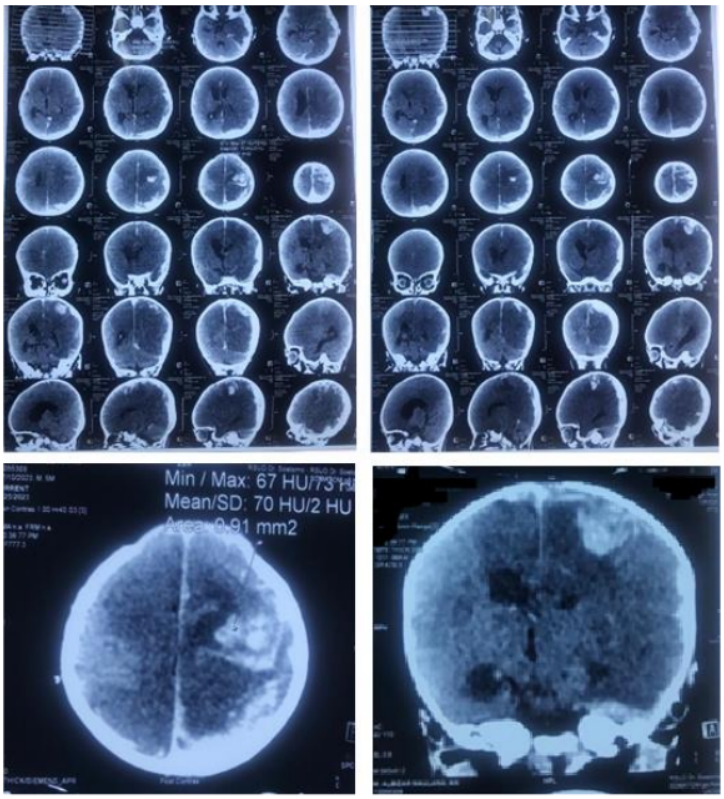

Fig. 3 HEAD CT-SCAN WITH CONTRAST BEFORE THERAPY.

A 2-phase abdominal ultrasound examination showed liver with size +/- 8.4 cm, sharp angles, flat edges, echo parenchyma intensity appears normal and homogeneous, no intrahepatic bile duct (IHBD) / extrahepatic bile duct (EHBD) dilation is visible, portal vein caliber +/- 0.35 cm, a. hepatica caliber +/- 0.10 cm (ratio HAD/PV: 0.28), v.hepatica appears normal, triangular cord sign (-), no visible subcapsular hepatic flow, no visible nodules/cysts/masses, gall bladder with preprandial size +/- 2.3 (length) x 0.97 (width) cm, no visible wall thickening, no visible stones/nodules/sludge, in postprandial gall bladder size was +/- 0.7 x 0.4 cm with a contractility index of +/- 93%, spleen has longitudinal length size +/- 6.18 cm, echo parenchyma intensity appears normal, no visible masses/cysts, pancreas has normal size, echo parenchyma intensity appears normal, no visible widening of the pancreatic duct, no visible masses/cysts/calcifications, right kidney with size +/- 2.22 x 5.18 cm, echo cortex intensity appears normal, sinus cortex boundary appears clear, no pelvicalyceal system ectasis, no stones/cysts/masses, left kidney with size +/- 2.1 x 5.4 cm, echo cortex intensity appears normal, sinus cortex boundary appears clear, no pelvicalyceal system ectasis, no

stones/cysts/masses, bladder was filled with sufficient fluid, no wall thickening, no masses/stones/cysts, no extraluminal free fluid echo intensity in the abdominal cavity and pelvic cavity. A 2-phase abdominal ultrasound revealed there was no evidence of biliary atresia (Figure 4).

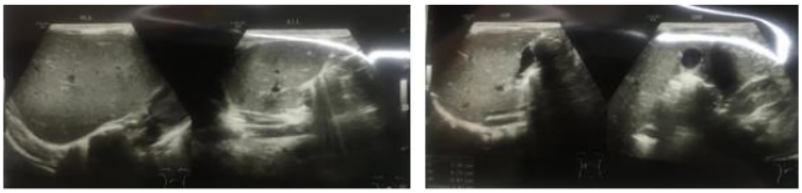

Fig. 4 A 2-PHASE ABDOMINAL ULTRASOUND EXAMINATION

Percutaneous liver biopsy examination results showed a piece of liver biopsy tissue consisting of 3 portal tracts. In the portal tract, there was no proliferation of bile ducts. There was a cluster of inflammatory lymphocyte and neutrophil cells in the portal tract that extended to the limiting plate (interface hepatitis). There was a focus on inflammatory lymphocyte, neutrophil, and histiocyte cells between hepatocyte cells. There were hepatic lobules consisting of hepatocyte cells and some had ballooning and cloudy degeneration. There were several dilated canaliculi containing bile pigment. There were several multinucleated giant cell hepatocytes. There were no signs of malignancy. On MT/RC staining, there was no fibrosis (F0). Percutaneous liver biopsy revealed intrahepatic cholestasis (neonatal hepatitis), without fibrosis.

This patient was given fresh frozen plasma (FFP) transfusion, vitamin K injection, seizure management according to the algorithm, mannitol to lower intracranial pressure, urso acid, and methylprednisolone. Clinical and laboratory monitoring was done and the improvement was good, however, long-term monitoring of growth and development was needed.

The patient was then followed up clinically and with supporting examinations, clinically, the patient's jaundice decreased. Blood laboratory examination after therapy showed hemoglobin level 12.3 g/dL, white blood cells level 11.65 x103/µL, platelet level 539 x103/µL, AST 69 U/L, ALT 154 U/L, Albumin 3. 87g/dL, Total Bilirubin 2.75 mg/dL, Direct bilirubin 2.43 mg/dL, ALP 444 U/L, GGT 462 U/L, and C-Reactive Protein (CRP) 0.20. The patient underwent clinical monitoring and routine evaluation of liver function tests. Currently, the patient is clinically well, with no jaundice, no abdominal distension, with normal growth and

development. The latest laboratory results showed a normal liver function test AST 72 U/L, ALT 92 U/L, total bilirubin 1.07 mg/dL, and direct bilirubin 0.45 mg/dL.

The monitoring was also performed with a head CT scan with contrast showed there is a hyperdense lesion with blood density (54 HU) measuring +/- 0.8 x 0.6 x 0.6 cm (volume +/- 0.14 cc) with a hypodense lesion with fluid density (26 HU) in the left frontal lobe accompanied by perifocal edema around it that presses and narrows the posterior horn of the left lateral ventricle. There was a hyperdense lesion with blood density (52 HU) with a hypodense lesion with fluid density (21 HU) with a maximum thickness of +/- 0.5 cm in the subdural space of the left temporoparietooccipital region. There was a hyperdense lesion with blood density (54 HU) that filled the subarachnoid space of the left temporooccipital region. Sulci effacement accompanied by loss of differentiation of white matter and gray matter with a large hypodense area in the right and left frontotemporoparietooccipital lobes (dominantly subcortical) which causes cerebellum density appear higher (pseudo hyperdense) compared to cerebrum (white cerebellum sign), ventricular system and cisterna outside the lesion appear normal, pons and cerebellum normal, no midline structure deviation, no abnormal calcification, no abnormalities in the right and left orbits, mastoids and paranasal sinuses with normal calvaria. Head CT Scan revealed intracranial hemorrhage (ICH) in the left frontal lobe (volume +/- 0.14 cc) partially resorbed with perifocal edema around it, partially resorbed subdural hemorrhage (SDH) in the left temporoparietooccipital region maximal thickness +/- 0.5 cm. It suggested left temporooccipital subarachnoid hemorrhage (SAH) and suspicious Hypoxic Ischemic Encephalopathy (Figure 5).

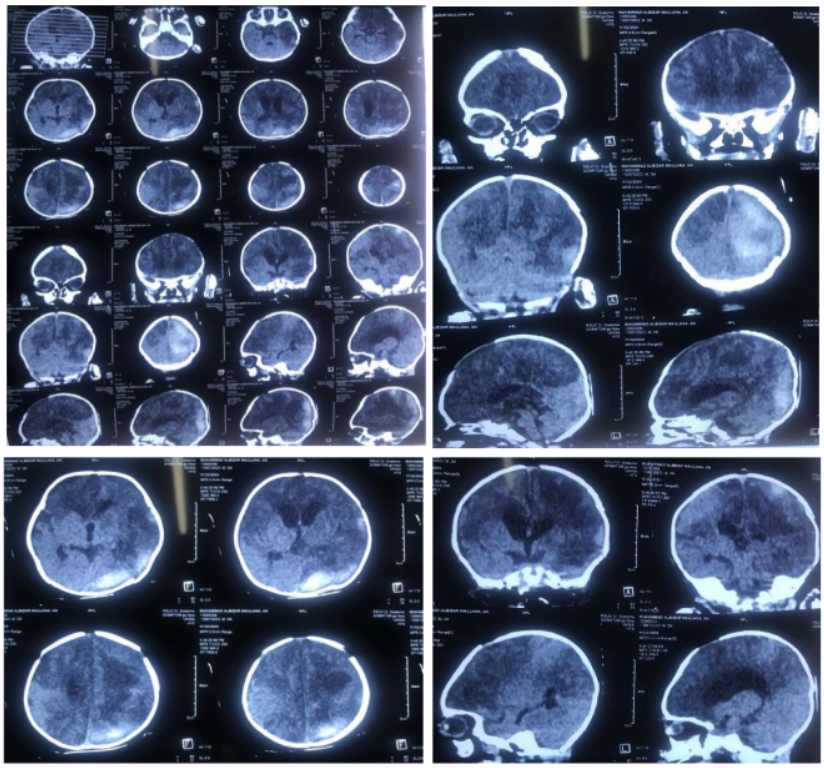

Fig. 5 HEAD CT-SCAN WITH CONTRAST AFTER THERAPY.

DISCUSSION

In this case, the patient came to the emergency department with bleeding signs in the form of bloody stools. The complaint was also accompanied by prolonged jaundice and pale stools. Physical examination revealed jaundice and hepatosplenomegaly indicating clinical signs of cholestasis. The suspicion of cholestasis was further strengthened by the findings of laboratory examinations that showed an increase in liver function levels (AST 160 U/L, ALT 150 U/L, total bilirubin 10 mg/dL, direct bilirubin 6.4 mg/dL, ALP 295 U/L, GGT 588 U/L, albumin 2.6 g/dL). Cholestasis is defined when the direct bilirubin level increases >1.0 mg/dL or >17mmol/L.[4]

Infants with cholestatic liver disease are at increased risk of secondary vitamin K deficiency due to impaired fat absorption and insufficient dietary intake. In cholestasis, the obstruction or reduction of bile flow hinders the emulsification and absorption of fat-soluble vitamins, such as vitamin K. This deficiency impairs the production of crucial vitamin K-dependent clotting factors (II, VII, IX, X), increasing the risk of coagulopathy in patients.[5]

Infants with cholestasis are particularly vulnerable to vitamin K deficiency bleeding (VKDB), which is marked by a heightened risk of spontaneous bleeding events, including gastrointestinal or intracranial bleeding. This condition can be life-threatening if not promptly managed with appropriate vitamin K supplementation.[2]

Vitamin K deficiency bleeding (VKDB) in infancy is categorized based on the timing of its occurrence: early (within 24 hours), classic (within the first-week post-birth), and late (between 2 weeks and 6 months of age). Late-onset VKDB in infancy poses significant risks and can be life-threatening. Consequently, it is essential that all infants, including those who are newborns, are administered vitamin K prophylaxis.6 The relationship between exclusive breastfeeding and cholestasis is strongly linked to this deficiency, leading to late-onset VKDB.[7]

There was the prolongation of hemostasis function (APPT 52.3 sec, PPT 44.1 sec). Peripheral blood smear showed anisopoikilocytic normochromic anemia, leukocytes with atypical lymphocytes and immature granulocytes, and thrombocytosis. The identification of VKDB is typically indicated by an extended APTT and prothrombin time (PT). VKDB is defined by a PT international normalized ratio (INR) of 4 or higher, or a value exceeding four times the normal range, alongside a normal platelet count and fibrinogen level. The diagnosis is validated through elevated levels of proteins induced by vitamin K absence or antagonists

(PIVKAs) and a swift normalization of coagulation parameters, including APTT and PT, following vitamin K administration, or both.[8]

The 2-phase abdominal ultrasound examination in this case showed no evidence of biliary atresia. However, a percutaneous liver biopsy examination showed intrahepatic cholestasis (neonatal hepatitis), without fibrosis. Studies indicated that secondary vitamin K deficiency can arise from factors such as chronic diarrhea, prolonged antibiotic treatment, and hepatobiliary conditions like biliary atresia and neonatal hepatitis.[9] Late-onset VKDB typically occurs in infants who are exclusively breastfed and have not been administered vitamin K prophylaxis at birth. This condition might also be linked to liver dysfunction resulting from neonatal hepatitis, bile duct atresia, or issues with intestinal absorption. Late-onset VKDB typically manifests with signs of intracranial bleeding in 30% to 60% of cases.[10]

The actual prevalence of vitamin K deficiency in cholestatic liver disease remains unclear, leading to ongoing debates about the necessity of routine supplementation. Vitamin K deficiency is common in children experiencing mild-to-moderate cholestatic liver disease, despite receiving vitamin K supplementation. The relationship between vitamin K deficiency and the extent of cholestasis, as well as the severity of liver disease in pediatric populations, is noteworthy.[3] Ensuring sufficient vitamin K levels in children suffering from cholestatic liver disease is essential for promoting proper coagulation and potentially aiding in brain development. Vitamin K deficiency poses a significant risk for children with cholestatic liver disease, potentially resulting in severe hemorrhage that could lead to disability or fatal outcomes.[11]

Since the patient had seizures in this case, a contrast CT scan of the head was performed. The results showed ICH in the left subcortical parietal, SDH in the subdural space of the left temporoparietal region, and in the left tentorium cerebelli, Left temporooccipital SAH. The conclusion is suspicion of Hypoxic Ischemic Encephalopathy. Studies indicated 11 infants diagnosed with cholestatic liver disease of various origins who presented with intracranial hemorrhage (ICH). The final diagnoses for the patients included BA in four cases, giant cell hepatitis in three, neonatal hepatitis in two, and cytomegalovirus hepatitis in two. The cholestatic liver disease must be taken into account when treating ICH resulting from vitamin K deficiency.[2] During long-term follow-up, a patient with BA presenting ICH was noted to have neurological sequelae, including developmental delay, cognitive impairment, and

epilepsy, which were observed in over half of the patients with ICH attributed to vitamin K deficiency.[12]

The patient received a transfusion of fresh frozen plasma, an injection of vitamin K, management for seizures following the established protocol, mannitol to reduce intracranial pressure, as well as urso acid and methylprednisolone. Monitoring in both clinical and laboratory settings was conducted, showing improvement; however, it is essential to implement long-term tracking of growth and development. No randomized trials have been conducted to assess the effectiveness of early postnatal intramuscular vitamin K in preventing late VKDB.[13] Nonetheless, numerous extensive national surveillance studies have investigated the incidence of late VKDB following the implementation of vitamin K prophylaxis in Japan, Germany, Great Britain, and Thailand. All of these studies have demonstrated notable decreases in late-onset VKDB within the population. The significant rates of mortality and morbidity, coupled with the near eradication achieved through prophylactic vitamin K, have positioned this issue as a central concern for public health initiatives globally.[10]

VKDB continues to be a significant issue in newborns and young infants. Administering vitamin K via injection has demonstrated the highest efficacy in preventing VKDB in neonates and young infants. The American Academy of Pediatrics (AAP) advises that all newborns weighing over 1500 g receive a single intramuscular dose of 1 mg of vitamin K within 6 hours of birth. Infants born preterm with a weight of ≤1500 g are recommended to be administered a single intramuscular dose of vitamin K ranging from 0.3 mg/kg to 0.5 mg/kg. Administering a single dose of intravenous vitamin K for preterm infants is not advised for preventive measures. VKDB must be taken into account when assessing bleeding during the initial 6 months of life, regardless of prophylaxis, particularly in infants who are exclusively breastfed.[10]

Previous studies indicated that in cases where vitamin K deficiency is suspected, immediate administration of vitamin K is essential, with prompt correction of PT and aPTT serving to confirm the diagnosis. Intravenous administration of vitamin K at a dosage of 0.5–1.0 mg/kg has been shown to enhance clinical bleeding tendency within one hour and to normalize coagulation within several hours.[2]

CONCLUSION

In conclusion, ICH in cholestasis patients is a rare but serious complication, often associated with coagulation disorders resulting from impaired liver function. Early recognition of the risk of VKDB in cholestatic patients is essential to prevent life-threatening hemorrhagic

events. Regular monitoring of coagulation profiles, along with timely supplementation of vitamin K, can significantly reduce the risk of intracerebral hemorrhage (ICH). Early detection of cholestatic in prolonged jaundice infants needs to be considered.

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