Vitamin K-Deficient Intracranial Hemorrhage as the First Symptom of Cytomegalovirus Hepatitis with Cholestasis

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YAMADA, K., FUKAO, T., SUZUKI, H., INOUE, R., KONDO, T. and KONDO, N. Vitamin K-Deficient Intracranial Hemorrhage as the First Symptom of Cytomegalovirus Hepatitis with Cholestasis. Tohoku J. Exp. Med., 2007, 212 (3), 335-339 —— Since vitamin K2 (VitK2) syrup prophylaxis has become a routine measure for neonates and young infants, the incidence of vitamin K deficiency (VitK-D) in infancy has markedly decreased. However, we recently experienced 2 infantile cases of VitK deficiency, in whom intracranial hemorrhage (ICH) was the first clinical sign of CMV hepatitis. Case 1 is a breast-fed boy who received VitK2 syrup orally at birth and at the age of 1 month. He did not suckle well and developed a generalized tonic convulsion twice at the age of 8 weeks. Case 2 is a mixed-fed boy who also received VitK2 syrup twice but developed vomiting and drowsiness at the age of 4 months. In both cases, laboratory tests showed anemia, leukocytosis, liver dysfunction with cholestasis, and coagulopathy, consistent with VitK-D abnormality. Their serological analyses showed that cytomegalovirus (CMV) IgG and IgM were both positive. In case 1, CMV DNA was positive, as judged by the PCR method. In case 2, CMV antigenemia was positive. Hence we diagnosed these two patients as having VitK-D ICH caused by CMV hepatitis with cholestasis. CMV hepatitis is a risk factor of VitK-D ICH. ——— cytomegalovirus; hepatitis; vitamin K; intracranial hemorrhage; cholestasis

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Vitamin K-deficient intracranial hemorrhage (VitK-D ICH) is a serious condition in infants. VitK2 prophylaxis became a routine measure for neonates so the incidence of VitK-D ICH has markedly decreased in Japan (Shirahata et al. 2002, 2006). There are several reports stating that VitK-D bleeding is the first clinical symptom of cholestasis (extrahepatic biliary atresia, chole-
dochal cysts, and α-1-antitrypsin deficiency) rather than prolonged jaundice (Merelle et al. 1960; Houwen et al. 1987; Bancroft et al. 1993; van den Anker and Sinaasappel 1993; Vorstman and Anslow 2003). We recently experienced 2 infantile cases of VitK-D ICH. They were later revealed to have cytomegalovirus (CMV) hepatitis with cholestasis. Infantile CMV hepatitis with
Intracranial Hemorrhage Induced by Cytomegalovirus Hepatitis with Cholestasis

The blood levels of amino acids were within normal ranges (citrulline 26 \( \mu \text{mol/l} \), phenylalanine 64.8 \( \mu \text{mol/l} \), methionine 53.2 \( \mu \text{mol/l} \)). Hence he was diagnosed as having CMV hepatitis-induced VitK-D ICH.

ICH was initially conservatively managed but gradually compressed the brain, hence on the 30th hospital day, surgical drainage was performed. He was discharged on the 50th hospital day, by which time CMV IgM (1.94) had declined. Mild liver dysfunction was improved by 2 years of age (T.bil 0.5 mg/dl, D. bil 0.4 mg/dl, AST 53 IU/l, ALT 23 IU/l). He is now 2 years old and his growth and development are within normal ranges.

Case 2
The patient, a 4-month-old boy, was transferred to our hospital for treatment of ICH. He was born at term after an uncomplicated pregnancy. Phototherapy was done for neonatal hyperbilirubinemia (T.bil 15.8 mg/dl). He received VitK2 syrup (2 mg) orally at birth and at the age of 1 month. He was breast- and artificial milk-fed and his patients did not recognize his dark urine and light stool color. At the age of 4 months, he was

In order to exclude other cholestatic hepatitis, we performed the following examinations. Antibodies for toxoplasmosis, rubella, herpes simplex, Epstein-Barr and hepatitis B viruses were negative. Abdominal CT and hepatobiliary scintigraphy revealed no evidence of biliary atresia or biliary dilatation. The blood levels of amino acids were within normal ranges (citrulline 26 \( \mu \text{mol/l} \), phenylalanine 64.8 \( \mu \text{mol/l} \), methionine 53.2 \( \mu \text{mol/l} \)). Hence he was diagnosed as having CMV hepatitis-induced VitK-D ICH.

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admitted to a local hospital due to vomiting and drowsiness. Brain CT showed a right subdural hemorrhage. Laboratory tests showed anemia (Hb 7.8 g/dl) and liver dysfunction with coagulopathy (T.bil 3.5 mg/dl, D.bil 2.3 mg/dl, AST 199 IU/l, ALT 223 IU/l, LDH 902 IU/l, total cholesterol 122 mg/dl, ALP 1448 IU/l, γ-GTP 100 IU/l, TBA 51 μmol/l, LAP 96 IU/l, PT < 4%, APTT 155.3 sec (reference time 30 sec), HPT < 5%). He received intravenous VitK2 (2 mg) and glycerol, and was then transferred to our hospital. On admission, he was unconscious (Glasgow Coma Scale 1-1-1), and had a tense anterior fontanelle. The ocular conjunctiva was slightly icteric and his liver was 2 cm palpable. The coagulation test slightly improved (PT < 40%, APTT 36.1 sec [reference time 30 sec]) at 3 hrs after administration of VitK2. Brain CT showed a massive right subdural hematoma with midline shift (Fig. 2). CMV IgM (4.06) was positive and CMV antigenemia (the number of CMV antigen-positive leukocytes: 2/1.5 × 10⁷ WBC) was detected.

Other virological examinations were negative as with case 1. Abdominal CT and magnetic resonance cholangiopancreatography revealed no evidence of biliary atresia or biliary dilatation. The blood levels of amino acids were within normal ranges (citrulline 18.8 μmol/l, phenylalanine 46.7 μmol/l, methionine 55.1 μmol/l). Hence, he was diagnosed as having CMV hepatitis-induced VitK-D ICH.

On the 2nd hospital day, surgical drainage was performed and he became conscious. On the 12th hospital day, liver dysfunction with cholestasis still persisted (T.bil 2.7 mg/dl, D.bil 1.4 mg/dl, AST 120 IU/l, ALT 265 IU/l, LDH 386 IU/l, γ-GTP 110 IU/l, TBA 116 μmol/L, PIVKA-II 2,300 mAU/ml). After high-dose γ-globulin therapy (100-400 mg/kg/day, 5 days) was done three times for prolonged liver dysfunction, his laboratory data improved and CMV IgM (1.0) had declined. He was discharged on the 125th hospital day. Mild liver dysfunction ceased by 1 year of age. He is now 3 years old and his growth and development are within normal ranges.

**DISCUSSION**

We presented here two cases of VitK-D ICH, both of which showed the first clinical symptoms of CMV hepatitis. Prolonged obstructive jaundice was not noted in either case. When ICH was apparent, laboratory tests showed coagulopathy consistent with VitK deficiency and also elevated transaminase with cholestasis. In both cases, evidence of CMV infection was obtained as an etiology of liver dysfunction. To our knowledge, only one premature infant and one mature infant had CMV hepatitis-caused VitK-D ICH (Loughnan et al. 1996; Yoshida et al. 2001). Therefore we thought that our reported cases were very rare.

Perinatal CMV transmission is common, reaching 10-60% by 6 months of age (Stagno 2000). Although the majority of infants remain asymptomatic, some develop CMV hepatitis. We clearly showed that our patients had active CMV infection when they developed hepatic dysfunction with cholestasis and VitK-D ICH, by CMV PCR, CMV antigenemia, and serum CMV IgM/IgG antibodies. Recent studies indicated that CMV PCR and CMV antigenemia may be sensitive with respect to early diagnosis of CMV infection in immunocompetent patients (Brytting et al.

One may point out the possibility that these patients had other disorders causing hepatitis with cholestasis and that CMV infection overlapped by chance. Although active CMV infection is best demonstrated by virus isolation from focus tissues obtained by biopsy (Stagno 2000), this procedure cannot be readily conducted in severely ill patients. We did not perform liver biopsy which could show direct evidence of CMV hepatitis. However, we could rule out most causes of cholestasis in these patients, such as idiopathic neonatal hepatitis, other viral diseases, metabolic diseases, intrahepatic bile duct hypoplasia or paucity, and extrahepatic biliary atresia. We, hence, believe that our patients had hepatic dysfunction with CMV hepatitis and cholestasis, which caused VitK-D ICH.

The oral VitK prophylactic failure rates per 100,000 live births (including cases given all recommended doses and those given incomplete prophylaxis) were 2.3 (95% CI 1.6-3.4) in Germany (December 1992-December 1994) and 2.5 (1.1-4.8) in Australia (January 1993-March 1994) (Cornelissen et al. 1997). In Japan, VitK prophylaxis has dramatically reduced the incidence of VitK-D ICH and a similar failure rate of 2.5 was seen in 1990 (Shirahata et al. 2002). According to the most recent nationwide survey of VitK deficiency in Japan (Shirahata et al. 2006), the incidence of infantile VitK-D bleeding was reduced to about one half of that in 1990. Shirahata et al. (2006) speculated that VitK prophylaxis three times had a beneficial effect on preventing VitK-D bleeding. VitK prophylaxis twice in our cases might be a risk factor of ICH.

There are several reports stating that cholestasis causes VitK-D ICH (Merelle et al. 1960; Houwen et al. 1987; Bancroft et al. 1993; van den Anker et al. 1993; Vorstman et al. 2003). The causes of cholestasis in these reports are extrahepatic biliary atresia, choledochal cysts, and alpha-1 antitrypsin deficiency. A pooled data analysis for late-onset hemorrhagic disease by Loughnan and McDougall (1993) showed that 55 cases in a total of 131 cases (42%) were associated with cholestatic liver diseases. Cholestatic-associated fat malabsorption is believed to cause VitK deficiency.

Since VitK2 prophylaxis has successfully reduced VitK-D ICH, secondary VitK-D ICH, such as that caused by CMV hepatitis with cholestasis, may become more evident in cases of VitK prophylactic failure. Sutor (2003) stated that daily or weekly oral administration of VitK could prevent this disease (including the secondary type) perfectly. One lesson from these cases is that daily or weekly prophylactic oral VitK administration is necessary for infants with CMV hepatitis having cholestasis. CMV hepatitis with cholestasis is a risk factor of VitK-D ICH.

References


