Intra-cranial hemorrhage in infants due to vitamin K deficiency – report of 2 cases

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Abstract

Objective: drive attention to the late form of the hemorrhagic disease of the newborn, secondary to vitamin K deficiency, as a cause of intracranial hemorrhage in young infants.

Methods: the authors describe and analyze two cases of late hemorrhagic disease of the newborn, secondary to vitamin K deficiency, producing intracranially hemorrhage during the second month of age. The most important publications on this subject are reviewed.

Results: Both infants had not received prophylaxis with vitamin K at birth. They were both being fed exclusively on breast milk. They developed intracranial hemorrhage, and the clotting defect was rapidly corrected with intramuscular vitamin K. At 3 and 4 years of age, one of them has showed normal psychomotor development, and the other has showed moderate developmental delay with microcephaly.

Conclusion: late hemorrhagic disease of the newborn must be considered in young infants, between 2 and 12 weeks of age, with intracranial hemorrhage, especially those fed exclusively on breast milk who did not receive vitamin K at birth. It may produce neurodevelopmental delay. The clotting defect is rapidly corrected with intramuscular vitamin K. This condition is preventable. The prophylaxis is recommended with 1 mg of intramuscular vitamin K to all newborns, at birth, even without risk factors.


Introduction

There is a consensus regarding the indication of prophylactic vitamin K in newborns who present risk factors for hemorrhagic diseases, such as diarrhea, cystic fibrosis, biliary atresia, alpha 1-antitrypsin deficiency, hepatitis, abetalipoproteinemia, maternal exposure to warfarin, anticonvulsant agents, and other drugs. It is methodologically difficult, however, to establish an exact risk-benefit ratio for this procedure in newborns who do not present these factors.1-2 The American Academy of Pediatrics and most European authors recommend that all newborns be submitted to prophylaxis, since the available evidence suggest that the benefit is higher than the risk.3-6 During the past years, the main discussions have focused on the form and regimen of administration.7-8
We present two representative cases of intracranial hemorrhage secondary to late hemorrhagic disease due to vitamin K deficiency in infants who did not receive vitamin K prophylaxis at birth and who were exclusively breastfed.

Case reports

Case 1

A 43-day old, white male newborn was admitted at Hospital Infantil Joana de Gusmão with fever, hypoactivity, moaning, and nasal cutaneous bleeding due to superficial wound in the previous 24 hours. There were no relevant prenatal antecedents. The baby did not have any problems during the neonatal period, and did not receive vitamin K prophylaxis at birth. He was fed exclusively with breast milk.

On examination, we observed cutaneous-mucosal pallor, hypoactivity, discrete jaundice, ecchymoses and petechiae on the palate, cutaneous bleeding in the nose due to small excoriation, bleeding in venopuncture areas, tense anterior fontanelle.

Hematocrit (Ht) was 28%, and hemoglobin (Hb), 9.1 mg/dl. Plaque count and leukogram were normal. Prothrombin time (PT) was prolonged (superior to 60 seconds and inferior to 10% of activity), activated partial thromboplastin time (APTT) was also prolonged (77 seconds), and the activity of VIII factor was 100%. Cerebrospinal fluid (CSF) presented 8 leukocytes/mm³, 64,000 erythrocytes/mm³, glycorrhachia at 51 mg/dl (glycemia at 72 mg/dl) and proteinorrhachia was 3.5 g/dl. A transfontanellar ultrasonography showed voluminous left frontobasal hematoma with left lateral ventricle and III ventricle flooding. These images were better defined through computed tomography (Figure 1).

The patient received erythrocyte concentrate, fresh plasma, and a 5 mg-dose of vitamin K (phytomenadione) intramuscularly. Ten hours after the admission, Ht was 12%, and hemoglobin was 4 g/dl, fontanelle remained tense. He started to have seizures, what made him receive phenytoin intravenously. As seizures persisted, he also took phenobarbital. Fresh plasma and erythrocyte concentrate were given in other occasions.

After 24 hours of admission, PT and APTT were stabilized. Ht and Hb were 30% and 10.3 mg/dl, respectively. In the ensuing 4 days, vitamin K was prescribed in a 5 mg-dose a day intravenously.

Clinically speaking, the evolution was fast and favorable, and he was discharged at the 5th day of hospitalization.

The cephalic perimeter control, as well as the control through ultrasonography, showed hematoma regression without hydrocephalus.

Nowadays, at the age of 3, his development has been adequate, and the neurological examination is normal.

Case 2

A 47-day old, white male infant was admitted to Hospital Infantil Joana de Gusmão in February, 23, 1995, reporting irritability during the 4 previous days. In the 9 hours that preceded the hospitalization, he presented recurring opisthotonos. At admission, we observed irritability, opisthotonos, fontanelle convexity and cutaneous-mucosal pallor. There were no relevant pre or perinatal antecedents. He was exclusively breastfed and did not receive vitamin K at birth. A lumbar puncture revealed xanthochromic and hemorrhagic CSF, with 396,000 erythrocytes/mm³, 1,886 leukocytes/mm³, with 13% of them being mononuclear, glycorrhachia at 3.7 mg/dl (glycemia 100 mg/dl), and proteinorrhachia at 640 mg/dl. Ht was 22%, and Hb was 7.6 mg/dl. We verified leukocytosis at 35,200 leukocytes/mm³, with 2% of bands, 70% of segmented leukocytes, 25% of Anticonvulsant agents were eliminated without recurring crises.

Figure 1 - Cranial computed tomography in case 1 showing extensive left frontobasal hematoma with left lateral ventricle and third ventricle flooding
lymphocytes, and 3% of monocytes. PT and APTT were prolonged. PT was superior to 60 seconds (inferior to 10% of activity), and APTT was 74 seconds. A transfontanellar ultrasonography revealed extensive cerebellar hematoma, with flooding of the ventricular system. A tomography defined these findings in a better way (Figure 2). The patient received a 1 mg/kg/day-dose of vitamin K intramuscularly during 5 days. He also received fresh plasma. Three hours after the administration of vitamin K and fresh plasma, APTT was normalized, and PT was 32 seconds (patient/normal ratio of 2.4). Twenty hours later, PT and APTT were normal. On the 1st day of hospitalization, he presented clear signs of intracranial hypertension, with bradycardia and respiratory pauses, which made him be submitted to external ventricular drainage during 23 days. Mechanical ventilation was necessary for 2 days.

He had seizures during the 1st week of hospitalization, and was treated with phenobarbital for 2 months. He developed ventriculitis due to a non-identified germ resulting from the complication of the external ventricular drainage, which was controlled in 3 weeks. He was submitted to ventriculo-peritoneal shunt on the 6th week of hospitalization. He was discharged after 45 days in hospital.

Today, aged 4, he presents microcephaly and moderate psychomotor retardation. No convulsive crises have occurred again, even without the use of antiepileptic drugs.

Discussion

Vitamin K is necessary for the synthesis of several proteins: the most well-known are the coagulation factors II, VII, IX, and X. Vitamin K acts in the conversion of glutamic acid into gamma-carboxyglutamic acid into vitamin K-dependent coagulation factors. These non-carboxylated proteins do not bind to calcium, being therefore ineffective.3,9

The levels of vitamin K-dependent coagulation factors in newborns correspond to 30 to 60% of those observed in adults. They increase mainly during the first 6 weeks of life.3 PT and APTT are therefore physiologically prolonged, and they are not adequate for the diagnosis of vitamin K deficiency in this period anymore. During the first months of life, the dosage of non-carboxylated proteins (PIVKA-II: protein induced by vitamin K absence or antagonist II) is the most specific test.4

The passage of vitamin K through the placental barrier requires high levels of maternal vitamin K. When the gradient is not adequate, vitamin K is deficient at birth.3

The concentration of vitamin K in breast milk is usually inferior to 20 mg/l, while in commercial formulae, this value is about 50 mg/l. Besides that, the intestinal flora of breastfed infants is not efficient in the synthesis of vitamin K, since lactobacilli do not seem to synthesize the vitamin.3,10

Three clinical forms of hemorrhagic disease in newborns due to vitamin K deficiency are described: the premature form, the classic form and the late form.3

The late hemorrhagic disease, verified in the cases described, usually takes place in a period ranging from 2 to 12 weeks of life in infants who are exclusively breastfed. Nervous system, skin, and gastrointestinal tract are the regions affected by the hemorrhage.5,11 Intestinal malabsorption, drugs used with pregnant women, and alpha 1-antitrypsin deficiency may be idiopathic or secondary. Some common characteristics have been observed in idiopathic cases:10 1) it is more frequent among Asiatic babies; 2) it is more common between the 1st and the 2nd months of life; 3) these infants are exclusively breastfed; 4) it is more common in boys; and 5) there is a high incidence of intracranial hemorrhage.

In our cases, disturbs that could produce a secondary vitamin K deficiency were not detected. These infants are consequently included in the group of late idiopathic hemorrhagic disease, with all the characteristics common to this group except for the ethnic/geographic origin.

Although it was not possible to perform the most specific test for the diagnosis of vitamin K deficiency at this age, which is the PIVKA-II dosage, the quick normalization of PT and APTT (within 24 hours) after the intramuscular and intravenous administration of the vitamin, associated with the clinical status, is enough for the diagnosis.10,12

Chaou et al.10 studied 32 infants, with ages ranging from 10 to 40 days in most of the cases, who presented intracranial hemorrhage due to vitamin K deficiency. During the follow-up period, they concluded that, except for one patient, all of them presented some degree of neurological dysfunction before turning 2. One of our patients presented quick and favorable evolution. Nowadays, aged 3, his development has been adequate, and it is not possible to detect any
neurological dysfunction. On the contrary, the second patient presents microcephaly and moderate psychomotor retardation, which may also be related to ventriculitis as a complication of the external ventricular drainage.

In 1961, the Nutrition Committee of the American Academy of Pediatrics had already recommended the parenteral prophylactic administration of a 0.5-1.0 mg-dose of vitamin K to all newborns.9

The incidence of late hemorrhagic disease in infants with no history of vitamin K prophylaxis varied from 4.4 to 7.2 per 100,000 births in Asiatic and European studies. When a single oral dose of vitamin K was administered at birth, this number fell to 1.4-6.4.5

In the 1990s, with the benefit of prophylaxis for all newborns, the discussion was resumed when Golding et al. suggested, in two studies,13,14 that the parenteral administration of vitamin K at birth could increase the incidence of childhood cancer, especially leukemia. In 1992, this possibility was soon questioned, with the verification that the rise in the sale of vitamin K in the United States during the 1960s did not increase cancer incidence.1 Recently, the association between vitamin K and cancer has been satisfactorily contested in several studies.15-17

The American Academy of Pediatrics recommends that every newborn receives from 0.5 to 1mg of vitamin K intramuscularly at birth. Oral prophylaxis in a 2 mg-dose at birth, between the 1st and 2nd week, and in the 4th week is an alternative. When the newborn develops diarrhea and is exclusively breastfed, prophylaxis must be repeated.5 Recently, Clark & James8 suggested that oral prophylaxis with a 2 mg single dose in normal newborns might be equally efficient. In Brazil, there are no commercial forms of vitamin K for oral administration, and the intramuscular administration of phytomenadione is the only choice for prophylaxis.

Vitamin K supplementation in pregnant women with risk for a premature delivery does not seem to prevent hemorrhage of the germinative matrix.18 In pregnant women who use hepatic enzyme-inducer anticonvulsant agents (phenobarbital, phenytoin and carbamazepine), vitamin K supplementation is recommended to be performed during the last weeks of pregnancy.19

References


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