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Intracranial Haemorrhage Due to Late-Onset Vitamin K Deficiency

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Abstract ***Objective:*** Deficiency of vitamin K predisposes to bleeding and it can be divided into early, classical, or late vitamin K deficiency bleeding (VKDB) according to their onset. Late VKDB occurs after 7th day of life at neonatal period and is associated with intracranial bleeding, serious neurological sequels and death. This retrospective study reviewed the clinical presentations, demographic features and radiological findings of infants with intracranial haemorrhage due to late-onset VKDB. ***Materials and methods:*** We identified 26 cases of late VKDB admitted to our hospital from February 1992 to November 2006. Cranial computerised tomography was performed in all patients at diagnosis and at subsequent evaluation. ***Results:*** Sixteen of twenty-six patients with late VKDB (61.5%) had intracranial haemorrhage (ICH). The mean age of these 16 patients with ICH was 1.6±0.7 months. All of them were on breastfeeding. Eighteen of them received one mg of vitamin K intramuscularly (IM) shortly after birth. None of them received any other medication. The most common sign and symptom of patients with ICH was bulging fontanel (69%). The most common bleeding site was parenchymal (n=7, 43.7%). The mortality rate was 44% among patients with ICH. ***Conclusion:*** For neonates on strict breast-feeding, despite some with vitamin K prophylaxis, some patients still may suffer from intracranial and extracranial bleeding due to vitamin K deficiency. Therefore, additional IM dose of vitamin K may be needed. However, further evidence from larger prospective study is needed to verify this observation.

Key words Children; Intracranial haemorrhage; Vitamin K deficiency bleeding

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Introduction

Vitamin K is a fat-soluble vitamin that is necessary for the synthesis of factors II, VII, IX, and X by the liver. Danish biochemist Henrik Dam, first described the K deficiency.[1,2] Vitamin K level in the newborn is low due to insufficient vitamin K stores and also lack of intestinal bacteria conversion in early life. In addition, vitamin K transfers poorly through the placenta from mother to infant and is available only at extremely low concentrations in human milk.[1-4]

Vitamin K deficiency bleeding (VKDB) has three distinct patterns of presentation. Early VKDB occurs within 24 hours of birth in infants whose mothers have been on anticonvulsant or warfarin during pregnancy. Classic VKDB occurs between 2nd-7th days of life with most of the cases being idiopathic. Late VKDB is characterised by bleeding in infants between 8th day to 6th months of life due to severe vitamin K deficiency. Late VKDB occurs

primarily in exclusively breastfeeding infants, and those with systemic illnesses. It has a peak incidence between the 3rd and 8th weeks of life.[2,3,5] In Turkey, all the infants only receive 1 (one) dose vitamin K at birth. There is no additional dose applying.

Late VKDB is associated with intracranial haemorrhage (ICH), which is the cause of severe consequence and death. It can occur in more than 50% of cases.[2,6] Despite being the best nutrient for infants, breast milk plays a significant role in the newborn classical and late-onset VKDB. Vitamin K administration at newborn decreases the incidence of VKDB in the first week of life. Furthermore, sporadic cases with late-onset disease have been reported in those who are exclusively on breastfeeding.[6,7] The current retrospective study is an analysis of the late VKDB data in an infant cohort. We aimed to emphasize the importance of additional vitamin K prophylaxis for prevention of late VKDB.

Materials and Methods

We retrieved the retrospective data of 26 patients with late VKDB who had been admitted to Ondokuz Mayıs University School of Medicine Pediatric Departments between February 1992 and November 2006. We performed in-depth analysis of 16 patients with ICH and late VKDB. Patients with prematurity and perinatal asphyxia were all excluded from the study. Details regarding pregnancy and delivery such as timing of presentation, place of birth (hospital or home), signs and symptoms, bleeding sites, underlying illness of the baby, laboratory results, management, outcomes, route of vitamin K administration at birth, types of feeding were all recorded. The diagnostic criteria of late VKDB were established by the following criteria: (a) bleeding in an infant after seven days of life; (b) normal levels of fibrinogen and platelet counts; (c) returning to normal levels of prothrombin time (PT) and activated partial thromboplastin time (aPTT) after vitamin K administrations which were both elevated before vitamin K administration. Laboratory results included complete blood count, clotting profile, liver function tests and urine analysis. Cranial computerised tomography and/or magnetic resonance imaging was performed to whom suspected with ICH. All cases were evaluated for possible complications for ICH. During the follow-up period; psychomotor assessments and neurological examinations were done in all patients. The study was approved by the local ethical committee of Bulent Ecevit School of Medicine in Zonguldak. Statistical analysis was performed using SPSS for Windows program, which was utilised to define number and percentage for discrete variables; furthermore, helped to count the mean and the standard deviation for continuous variables.

Results

Of 26 infants that fulfilled the diagnostic criteria of late VKDB, 16 (62%) were males and 10 (38%) were females. The age range of all patients with late VKDB was between 24th and 81st days of life. Sixteen of 26 patients were diagnosed to have ICH. The mean age of those 16 patients with ICH was 1.6±0.7 months. All patients were on breastfeeding. None of them was on any other medication (Table 1). All of the patients were full-term babies. Eighteen cases, which were born at the hospital, received one mg of vitamin K IM shortly after delivery, as a routine of practice in Turkey. The eight who delivered at home, did not receive any vitamin K prophylaxis. There was no history of any antithrombotic and anticonvulsant drug intake in the mothers, additionally family histories of the patients were negative for any bleeding disorder. The signs and symptoms of the patients at presentation of bleeding were bulging fontanels (69%), irritability (50%), convulsions (42%), bleeding and ecchymosis (39%), feeding intolerance, poor sucking (61%), diarrhoea (11%), and pallor (46%) (Table 2). Before treatment, PT and aPTT values were significantly prolonged in all cases. After administration of vitamin K, PT and aPTT levels return to normal levels. Platelet counts and blood biochemistry, including liver function parameters (e.g. bilirubin values) were all within the normal range for all patients. None of them had any liver or gastrointestinal disease. ICH was detected in 16 patients (61.5%). The haemorrhagic areas were subdural (SDH) in one (6.2%), subarachnoid (SAH) in one (6.2%), parenchymal (IPH) in seven cases (43.7%), intraventricular (IVH) in one (6.2%),

Table 1 General characteristics of the ICH cases

Characteristics	Mean ± standard deviation
Age (month)	1.6±0.7
Duration of symptoms (day)	3.2±0.7
Prothrombin time (second)	68.4±40.6
Activated partial thromboplastin time (second)	108.7±52.3
Follow-up period (month)	9.3±4.9

intracerebral plus intraventricular in four cases (25%), intracerebral (ICEH) plus subdural in one case (6.2%), and combination of intracerebral, subdural, and intraventricular in one case (6.2%). The cerebral imaging results and follow up results were presented at Table 3. All cases were treated with one mg intramuscular vitamin K and fresh frozen plasma. Five patients were transferred to the neurosurgery department for surgical treatment, and the others were followed with supportive therapy. Seven of 16 (44%) patients with ICH died. The remaining nine (56%) had a mean follow-up period was 9.3±4.9 months. Seven of 16 patients with ICH had some neurological problems such as epilepsy and mental motor retardation. During the follow-up period, four patients developed hydrocephaly, and 3 of them were operated for ventriculoperitoneal shunt replacement. One family, however, declined the shunt placement after being informed of the risks and benefits of the operation. Only one of them remained totally healthy, and the other two patients defaulted from their out-patient follow-up.

Table 2 Initial symptoms and sign of late vitamin K deficiency bleeding

Symptoms and sign	Number	Percent
Fontanel bulging	18	69
Irritability	13	50
Convulsions	11	42
Ecchymosis, other bleeding	10	39
Feeding intolerance, poor sucking	16	61
Diarrhoea	3	11
Pallor	12	46

Discussion

VKDB caused by vitamin K deficiency has a significantly high rate of morbidity and mortality.[3] VKDB is one of the most common causes of acquired haemostatic disorder in early infancy.[2,3] The name change from "haemorrhagic disease of newborn" (HDN) to VKDB was recommended by the International Society on Thrombosis and Haemostasis (ISTH) Pediatric/Perinatal Subcommittee in 1999. They clarified the aetiology that was solely based on vitamin K-deficiency, and they included the infants who develop VKDB beyond the 4-week newborn period.[5] Late VKDB may occur at any time between the 8th day and 12th months, but is more frequent at 4th-8th weeks of life.[1,2] It is often presented with intracranial haemorrhage and widespread deep ecchymosis. Additionally, gastrointestinal system and superficial skin haemorrhage had been reported.[6,8,9] The vitamin K content of breast-milk is extremely low compared with standard infant formulas.[1,10,11] It is well-known that administration of vitamin K parenterally to the newborns at birth can potentially prevent the occurrence of lethal haemorrhagic disease of the newborn. However, there are some controversial reports on what may be the optimal dose and method of administration.[1,3,6]

Cornelissen et al[12] compared three basic strategies for vitamin K prophylaxis for healthy newborns in Netherlands, Australia, Germany, Switzerland. They suggested the

Table 3 Cerebral imaging results and follow-up of patients

Localisation of intracranial haemorrhage	Number	Percent	Follow-up
Subdural haemorrhage	1	6.2	Death
Parenchymal haemorrhage (5 intracerebral, 2 intracerebral + intracerebellar)	7	43.7	3 epilepsy, 1 healthy, 2 death, 1 lost to follow-up
Intraventricular haemorrhage	1	6.2	Death
Subarachnoid haemorrhage	1	6.2	Death
Intracerebral haemorrhage + subdural haemorrhage	1	6.2	Death
Intracerebral haemorrhage + subdural haemorrhage+ intraventricular haemorrhage	1	6.2	Hydrocephalus + MMR
Intracerebral haemorrhage + intraventricular haemorrhage	4	25	3 hydrocephalus+ MMR (1 of 3 lost to follow-up), 1 Death

MMR: motor and mental retardation

success-rate of prophylaxis was 98.2%-100%. Six of the patients had late VKDB, although they had received a single-dose vitamin K at birth for prophylaxis. The compliance of the prophylactic regimen in Turkey does not seem to be as satisfactory, so we suggest a repetitive IM dose of vitamin K, especially for those infants solely on breastfeeding. We believe that it may reduce the high mortality rates of late VKDB in Turkey. However, its actual effectiveness requires further evidence to support.

The rates of late VKDB range from 4.4 to 7.2 cases per 100,000 births, based on reports from Europe and Asia.[1,2,12-19] In developed countries. VKDB is now a rare life-threatening disease due to the widespread use of effective prophylaxis with vitamin K at birth.[1,2,4,17] The postnatal administration of vitamin K dramatically decreased the incidence of vitamin K deficiency bleeding during the first weeks of life, although sporadic cases with late-onset haemorrhage were reported almost exclusively among breast-feeding infants who did not receive additional prophylaxis.[7] Routine vitamin K administration as prophylaxis at birth decreased the incidence of late VKDB from 7/100,000 to 1.1/100,000 live births in the Netherlands.[12] In a similar trial which evaluated the efficacy of routine vitamin K prophylaxis at birth between1998-2008; the overall VKDB incidence was found to be 24 per 100,000 births.[20] In New Zealand, VKDB is virtually confined to fully breastfeeding infants who were not given vitamin K at birth. Late-onset cases were frequently associated with liver disease.[20]

The practice of breastfeeding without any vitamin K prophylaxis at birth was reported to be the most common reason of late VKDB in previous studies. The main circulating form of vitamin K is phylloquinone. The concentration of vitamin K in human breast milk is low. The phylloquinone level is between 1-2 mcg/L in breast milk and is 55 mcg/L in formula.[2,21] On the other hand, the rates of breastfeeding without any supplementation were reported from Turkey as 93.5% and 97.5%, respectively.[3,6] In a study from India, of total 42 patients with late-onset VKDB, 76% of them were on breastfeeding and 81% were delivered at home.[8] We are presenting 26 patients with late-onset VKDB who were all on breastfeeding. While breast milk remains the best nutrient for the infants, our findings should not discourage mothers from breastfeeding due to the low vitamin K levels. This situation can be effectively resolved by vitamin K prophylaxis.

In the recent study, eighteen patients who were born at the hospital received one mg of vitamin K intramuscularly shortly after delivery. The rest that who were delivered at home did not receive any vitamin K prophylaxis. Currently, the rate of prophylactic vitamin K administration in Turkey has increased. The number of home births is on a decreasing trend in Turkey. On the other hand, even the World Health Organization recommends cesarean section rates should be lower than the rates of normal delivery, the cesarean rate has been progressively increasing in Turkey, from 6.9% (1993) to 14.0% (1998), 21.2%(2003), and 36.7% (2008) respectively.[3,22] We speculate that the increased rates of vitamin K prophylaxis might be associated with the increasing number of cesarean section and national health advocate on prophylaxis practice.

Late VKDB can present as convulsions, poor sucking, irritability and pallor. D'Souza and Rao[23] from India recorded convulsions in 71% and pallor in all their patients. In a study from Turkey that enrolled 120 cases, convulsions and irritability rate was 50%; and feeding intolerance, poor sucking, vomiting were seen in 46% of patients.[3] In another study, pallor (77.5%) and convulsions (58%) were the most common presenting features among the patients.[6] Feeding intolerance, poor sucking are the most common findings in this study with the rate of 61% and with a lesser extent of 46% for pallor and 42% for convulsions. Although haemorrhages from gastrointestinal system, mucosal membranes and skin can accompany the disease, intracranial haemorrhage is the main cause of morbidity and mortality.[6,24] At this study, 7 of 26 (27%) patients with late VKBD died. Forty-four percent of patients had ICH. Two-thirds of babies with late VKDB presented with serious intracranial bleeding leading to high morbidity and subsequent mortality.[1,2] Haemorrhage rates range between 54% and 88%; and mortality rates range between 22% and 33% from various Turkey studies.[3,6,10,25,26] In a study from Turkey, 73% of the patients had neurologic impairment, and mortality rate was 33%.[12] Similarly, a study with 30 patients, a mortality rate of 33% was observed.[14] Another study, including 14 cases in India showed that 88% of their cases had intracranial bleeding, and mortality rate was 57%.[8] The largest series in the literature which was published in 1998 had an ICH rate of 82%. On the other hand, intracranial haemorrhage was identified in 61.5%, and the mortality rate and neurological complication rates in patients with ICH were 44%. A total of 8 patients who were borne at home and did not receive vitamin K administration had ICH, we cannot determine the occurrence rate since the denominator remains unknown.

Intracranial haemorrhage risk of late VKDB was reported in as high as 50-80% of patients.[2] While subdural is the most common location for haemorrhage; subarachnoid place is the second most common location for haemorrhage.

Pooni et al[8] reported 57.2% had subdural haemorrhage, and subarachnoid haemorrhage was 46.4% of the patients. Martín-López et al[15] found that the majority of the patients developed haemorrhage in more than one site (75%). Özdemir et al[3] also agreed subdural haemorrhage was the most common (28%) haemorrhagic area in their report. In contrast to the literature, we found that the parenchymal area (44%) was the most common location for haemorrhage, and ICEH + IVH ranked 2nd for haemorrhage. There are some reports from Turkey that indicate the parenchymal area as the most common site for haemorrhage.[6,28]

Vitamin K deficiency can also occur due to secondary reasons. For instance, chronic diarrhoea, celiac disease, biliary atresia, cystic fibrosis, alpha 1-antitrypsin deficiency, abetalipoproteinemia and a history of maternal warfarin usage for a long period may induce vitamin K deficiency.[1,2,23] In the recent study, we did not detect any of these conditions mentioned above. Newborns only have 20-50% levels of adult coagulation activity. Lack of vitamin K administration at birth, diarrhoea, and prolonged use of antibiotics make them prone to bleeding associated with vitamin K deficiency. In this study, 3 of the infants had diarrhoea, but none required antibiotics usage.

During the follow-up period, three cases developed epilepsy, and four patients had motor and mental retardation. Hydrocephalus was diagnosed in four cases, and three of those four patients underwent ventriculoperitoneal shunts operation. Seven of the patients with ICH died (44%). Of a total of 691 cases of late VKDB reported in Thailand, the prevalence of ICH was 82% with a mortality rate of 24%, and about 50% of the survivors suffered from permanent neurological deficits.[27] Incidence of complications was reported to be around 36% by D'Souza and Rao[23] and was reported to be 29% by Pirinccioglu et al.[6] Similarly, we found the neurological impairment was up to 27% overall of our patients. Meanwhile, the frequency of ICH was 44%.

Conclusion

In summary, this study evaluated the prognosis and clinical features of infants with late-onset VKDB based on the data collected during a 14-year period. Additionally, the hospital births are gradually increasing for the last decade in Turkey. Our results postulate that late-onset VKDB remained a major cause for mortality and morbidity for neonates. Physicians should be aware about the importance of early use of vitamin K when necessary. We conclude hospitalisation for delivery and vitamin K administration at birth is highly crucial. Despite receiving one mg vitamin K administration at birth, we still observed ICH in these patients. Hence, further evidence from prospective study on a large population cohort should address the potential benefit of additional vitamin K administration. This knowledge may reduce the mortality and morbidity rates associated with VKDB in breastfeeding infants. A few countries such as the UK, Germany and Netherlands have surveillance schemes in place to monitor the effectiveness of vitamin K prophylaxis. We need similar surveillance programmes for the monitoring of the vitamin K applications.

Declaration of Conflicts of Interest

There is no conflict of interest to declare.

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