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Late haemorrhagic disease of the newborn

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Abstract

Background: Late haemorrhagic disease of the newborn (HDN) can occur owing to a lack of vitamin K prophylaxis, as a manifestation of an underlying disorder or idiopatically from the 8th day to 12 weeks after birth.

Methods: Eight infants admitted to Kocaeli University Hospital with nine episodes of late HDN between January 2002 and April 2005 were evaluated retrospectively from hospital records.

Results: The median age at presentation was 46 (26–111) days. All the infants were born at full-term to healthy mothers and were exclusively breast-fed. All had an uneventful perinatal history, except one who had meconium aspiration. Four patients had received no vitamin K prophylaxis and another three had uncertain histories. At presentation, six had intracranial bleeding and the remainder had bleeding either from the venepuncture site or the gastro-intestinal tract. The presenting signs and symptoms were irritability, vomiting, bulging or full fontanelle, convulsions and diminished or absent neonatal reflexes. Galactosaemia was detected in a 2-month-old infant with prolonged jaundice. There was no surgery-related mortality or complications but one survived for only 2 days on ventilatory support following surgery. Only one of the six survivors had severe neurological sequelae.

Conclusions: Late HDN frequently presents with intracranial haemorrhage, leading to high morbidity and mortality. HDN can be the manifestation of an underlying metabolic disorder. Vitamin K prophylaxis of the newborn should be routine in developing countries.

Introduction

Late haemorrhagic disease of the newborn (HDN) can occur owing to a lack of vitamin K prophylaxis, as a manifestation of an underlying disorder or idiopatically in the period 8 days to 12 weeks postnatally. Underlying disorders include diarrhoea, cystic fibrosis, biliary atresia, α 1-antitrypsin deficiency, hepatitis, abetalipoproteinaemia, Alagille's syndrome and galactosaemia. Vitamin K deficiency bleeding, previously known as haemorrhagic disease of the newborn (HDN), comprises early (0–24 hours), classical (1–7 days) and late (8 days to 12 weeks) syndromes, according to the time of presentation.[1,2] Since the introduction of routine vitamin K prophylaxis for newborns, the incidence of the classic form has decreased dramatically.[3,4] Nevertheless, an increase in the late form has been observed in developed countries[5] and is recognised worldwide as a significant cause of infant morbidity and mortality. Its sudden and unpredictable onset and the high percentage (50–82%) of intracranial haemorrhage as a presenting feature[6] are of major concern. We present eight infants with nine episodes of severe haemorrhage owing to late HDN.

Methods

This retrospective study was performed in the Department of Paediatrics, Kocaeli

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University Hospital, which is the only tertiary care centre in Kocaeli. Hospital records for 4916 children (<18 years) hospitalised between February 2002 and April 2005 were reviewed for detection of HDN. Vitamin K deficiency was diagnosed as the cause of coagulopathy if (a) the platelet count and fibrinogen were normal and fibrin degrading products were absent, (b) prothrombin time (PT) and aPTT were prolonged initially but returned to normal after vitamin K administration. If fresh frozen plasma was also administered, 7th-day PT and aPTT control must be normal to exclude the effect of transfused factors.

Data on age, gender, socio-economic level, consanguinity, vitamin K prophylaxis, underlying disorders, signs and symptoms, bleeding sites, laboratory assays, management and outcome were recorded from the charts, and information about the current status of the surviving infants was collected directly from the families over the telephone.

Results

Eight infants (five boys) with nine episodes of late HDN were detected. There was no early or classical HDN in the study period. The median age at presentation was 46 (26–111) days. All the infants were born at full-term to healthy mothers with a median birthweight of 3100 g (2700–3300) and were exclusively breast-fed. All were delivered in hospital. Except for one baby with meconium aspiration, all had uneventful perinatal histories. One had vitamin K prophylaxis, four had no prophylaxis and in three a history of vitamin K prophylaxis was uncertain. The parents of three patients were of middle and the rest of lower socio-economic status. Three sets of parents were consanguineous.

Clinical features, bleeding sites, surgical therapy and outcome are shown in Table 1. Patient 4 had a history of diarrhoea in the preceding 10 days and received 3 days of antibiotics. PT and aPTT were prolonged in all patients (median PT 120, range 52.8–200 sec, aPTT 120, range 71.5–350 sec). Haemoglobin (Hb) values at presentation were median 6.3 g/dl (range 4–10.2 g/dl) and platelets were within the normal range. All six patients with intracranial bleeding had computerised tomography (CT) imaging and underwent surgery. Mortality from bleeding was 12.5% (1/8, patient 1). There was no surgery-related mortality but patient 1 survived for only 2 days on ventilatory support following surgery. PT and aPTT remained normal in the follow-up period in patients without underlying metabolic disease. Patient 8 had galactosaemia and cholestasis that caused vitamin K deficiency. The survivors had no recurrent bleeding episodes in the follow-up period [mean (SD) 365 (385) days, median 275 (7–1217)].

Case Reports (Patients 4 and 8)

Patient 4, a baby boy who had received no vitamin K prophylaxis, was admitted with two episodes of bleeding on the 38th and 51st days. In the first episode, the bleeding was from a venepuncture site. On the 3rd postnatal day he had jaundice and had venepuncture on days 12 and 38 for determination of bilirubin levels. In addition, his mother gave a history of fresh blood in the stool on days 15 and 30 which resolved spontaneously. On first admission, his laboratory evaluation showed the following results: Hb 10.2 g/dl, platelet (PLT) count 369×10^9/L, PT 120 sec, INR 19.5, aPTT 120 sec, fibrinogen 3.53 g/dl, indirect bilirubin 86 mmol/L, direct bilirubin 24 mmol/L, alanine aminotransferase (ALT) 25 U/L, AST 59 U/L. He was the firstborn child. Results of investigations for haemolytic disease of the newborn and for thyroid functions were normal and the jaundice resolved spontaneously within a few days. Liver function tests were within normal limits. Coagulation factor levels after vitamin K administration, during follow-up

and between the episodes were normal [ALT 24 U/L, AST 36 U/L, total bilirubin 16 mmol/L, albumin 43 g/L, globulin 18 g/L, PT 12.4 sec, aPTT 32.5 sec, INR 1, fibrinogen 2.53 g/L, factor (F) II 76%, FV 169%, FVII 126%, FVIII 179%, FIX 74% and FX 73%]. The second admission was with intracranial bleeding. There was a 10-day history of diarrhoea and upper respiratory tract infection which was treated with oral azithromycin for 2 days, followed by two doses of intramuscular injection of ampicillin-sulbactam. PT and aPTT were again prolonged with normal fibrinogen, platelets, transaminases, bilirubin, albumin and total protein levels. The infant had no episode of bleeding in the follow-up period.

Patient 8 presented with prolonged jaundice and was evaluated for an inborn error of metabolism. On postnatal day 60, she presented with a history of irritability, vomiting and convulsions. On admission

TABLE 1. *Clinical and laboratory features, treatment and outcome.*

Patient	Gender/age (d) during bleeding	Vit. K prophylaxis	Clinical signs, symptoms	Bleeding site	Surgical intervention	Prognosis, follow-up period
1	M/53	?	Ecchymoses, vomiting, bulging fontanelle, facial paralysis, convulsions	Skin, left fronto-parietal parenchyma	Craniotomy, evacuation	Died, 7th day
2	F/35	?	Oozing from injection site	Right rectus femoris muscle	-	No sequelae, alive, 430 d
3	M/48	-	Ecchymosis on the trunk, haematemesis	Skin, upper GI tract	-	No sequelae, alive, 365 d
4	M/38, 1st attack	-	Oozing from venepuncture site, haematemesis	Brachial vein, lower GI tract	-	Mild right arm paralysis
	111, 2nd attack		Lethargy, hypoactivity, poor sucking	Left frontal cerebral parenchyma, left fronto-tempero-parietal and inter-hemispheric subdural area, midline shift	Craniotomy, evacuation	Alive, 494 d
5	M/44	?	Haematemesis, grunting, convulsions	Upper GI tract, right fronto-parietal subdural haematoma	Craniectomy, evacuation, subsequent cranioplasty, VP shunt	Severe neuromotor retardation, microcephaly, alive, 166 d
6	F/26	-	Vomiting, ecchymoses, bulging fontanelle	Skin, ventricular system, hydrocephalus	External drainage	No sequelae, alive, 1217 d
7	M/60	+	Convulsions, bulging fontanelle	Right frontal haematoma, midline shift	Craniotomy, evacuation	No sequelae, alive, 185 d
8*	F/60	-	History of poor sucking, irritability, jaundice, vomiting, convulsions, coma, anisocoria, bulging fontanelle, hepatomegaly on admission	Right fronto-parietal subdural haematoma	Craniectomy, evacuation	Died owing to underlying disease, 60 d

* Underlying metabolic disease was galactosaemia; VP, ventriculoperitoneal; GI, gastro-intestinal.

she was unconscious and physical examination showed jaundice, hepatomegaly and anisocoria. Her parents were cousins. Initial laboratory data were as follows: Hb 6.2 g/dL, PLT 252×10^9/L, PT 120 sec, aPTT 120 sec, AST 132 U/L, ALT 112 U/L, alkaline phosphatase 1496 U/L, GGT 96 U/L, total bilirubin 81 mmol/L, direct bilirubin 52 mg/dL, albumin 32 g/L, fibrinogen 2.5 g/L, FII 17%, FV 96%, FVII 20%, FIX 16%, FX 20%. She had reducing substance in the urine (Benedict's test positive, dipstick negative) and diagnosis was confirmed by chromatographic assay. There was no hypoglycaemia. She was referred to the Department of Metabolic Disorders and commenced on a lactose-free diet. She had no sequelae of intracranial bleeding. At her last attendance at outpatients at the age of 4 months, her liver functions were progressively worsening (direct bilirubin 142 mmol/L, indirect bilirubin 59 mmol/L, ALT 319 U/L, AST 593 U/L, PT 22.6 sec, INR 1.99, aPTT 45.9). Intramuscular vitamin K was administered but she died at home from complications of the underlying disease.

Discussion

Pathogenesis of HDN

Vitamin K is necessary for the synthesis of several coagulation factors (II, VII, IX and X). The levels of vitamin K-dependent coagulation factors in newborns correspond to 30–60% of those observed in adults. They increase mainly during the 1st 6 weeks of life. 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.[4] The concentration of vitamin K in breastmilk is usually <20 mg/L while, in commercial formula, this value is about 50 mg/L. Besides that, the intestinal flora of breast-fed infants is not efficient in the synthesis of vitamin K, since lactobacilli do not seem to synthesise the vitamin.[4,7]

Prophylaxis and incidence

The efficacy of neonatal vitamin K prophylaxis (oral or parenteral) in the prevention of classic HDN is firmly established. It has been the standard care since the American Academy of Pediatrics recommended it in 1961.[8] Some common characteristics have been observed in idiopathic late HDN:[7] it is more common in Asian babies, between the 1st and 2nd months of life, in exclusively breast-fed infants and in boys, and there is a high incidence of intracranial haemorrhage.

In Asian and European studies, the incidence of late HDN with no history of vitamin K prophylaxis varied from 4.4 to 7.2/100,000 births.[9] When a single oral dose of vitamin K was administered at birth, this number fell to 1.4–6.4.[9] Between 1980 and 1990, 108 cases of late HDN were reported from Germany.[2] The peak age was 4 weeks; the majority (79%) of the infants were aged between 3 and 7 weeks and 58% suffered intracranial bleeding, which resulted in a total mortality rate of 19% and neurological damage in 21%. At least 37% had cholestasis.

Some studies have reported that administration of a single dose of oral or parenteral vitamin K could not prevent late HDN.[10,11] Data from Denmark,[12] The Netherlands[13] and the United Kingdom[14] indicate that multiple doses had additional benefits. Findings in the UK study[14] and the known physiology of vitamin K suggest that even three oral doses might not provide sufficient protection in infants with underlying cholestasis. K_1 differs from other fat-soluble vitamins in that it has limited tissue reserves and is rapidly catabolised, with 60–70% of a single dose being excreted via the urine and bile within about 3 days.[15,16] Unless there are additional unknown factors that limit excretion under conditions of deficiency, it might be predicted that the length of protection afforded by a given dose is proportional to the fraction absorbed. Thus, although oral K_1 administration might improve vitamin K status in infants

with latent cholestasis in the short term, the absorbed dose will be insufficient to afford a buffer of reserves for longer term protection. In contrast, it has been suggested that the effectiveness of a single intramuscular dose of K_1 is owing to a depot effect and consequent delayed release of the highly lipophilic vitamin from muscle tissue.[17]

Intramuscular administration at birth of 1 mg vitamin K_1 (Konakion®, phytomenadione) is standard care in Turkey, but it can be neglected, especially with home deliveries and in some hospitals. In the present study, patient 7 had late HDN although parenteral vitamin K_1 was administered at birth. There are similar cases in the literature.[5] Since there is not a registry of HDN in Turkey, the incidence can not be estimated. In our city, almost all babies are delivered in government hospitals. The birth rates in these hospitals are very high and there is not a well established system for recording vitamin K administration. No verbal information or report is given to parents at discharge. During admission with HDN to our centre, the only way of knowing whether vitamin K prophylaxis has been given is the mother's observation that the baby had an intramuscular injection or a scar of injection at discharge. Three of the mothers were not sure of the presence of a scar. In the study period, 59,826 live births were recorded in the city. The incidence of late HDN in admissions to our centre was approximately 13.37/100,000 births.

In addition to infants with overt underlying disease causing liver dysfunction or malabsorption of fat-soluble vitamins, there are idiopathic cases. These are owing to a self-correcting disorder of liver function that leads to a degree of cholestasis and impairment of vitamin K absorption.[5] A daily oral dose in the 1st year might be effective in mimicking artificially vitamin-fortified infant formulae because even multiple doses of a better-absorbed oral mixed micellar preparation (3×2 mg, at birth, on days 3–10 and in weeks 4–6) did not prevent late HDN.[18] After administration of 1 mg vitamin K intramuscularly at birth, low-dose daily drops added to vitamin D drops would be the best option physiologically, but such an oral preparation has not yet been produced commercially.

Surgical intervention

Because there have been few studies of its effectiveness in HDN, surgical intervention for spontaneous intracerebral haemorrhage in infants is controversial. The major indications for it are extensive haemorrhage with radiographic evidence of mass effect (midline shift >0.5 cm) or evidence of cerebral herniation with signs of increased intracranial pressure. Surgery should be considered immediately when there is progressive deterioration of neurological status or focal neurological deficit (hemiparesis) in the presence of radiological evidence of significant mass effect.[19,20] Although open fontanelles and cranial sutures of infants have a positive impact in compensating for raised intracranial pressure, infants with intracerebral haemorrhage might still require surgical intervention in the above-mentioned situations. Surgical interventions for spontaneous intracerebral haemorrhage in infants are craniotomies or decompressive craniectomies with complete haematoma evacuation. Cerebroventricular or cerebrospinal fluid drainage systems are considered for intraventricular haemorrhage. It must be borne in mind that, in such cases, the immature brain requires appropriate anaesthesis and infants should be treated in settings where critical care is available. Craniotomy in young infants requires an appropriate team of experienced personnel.[20]

In a series of 11 full-term infants aged 1–70 days with spontaneous intraparenchymal haemorrhage owing to different aetiologies, eight with the above indications underwent surgical haematoma evacuation.[19] Of three infants with haemorrhage without mass effect who were not surgically treated, two showed speech delay during long-term

follow-up. Similar neurological abnormalities were seen in patients who underwent evacuation of haematomae.

In the present series, all six patients with intracerebral haemorrhage underwent surgical intervention owing to mass effect, signs of increased intracranial pressure and neurological deterioration. No patient had a post-operative wound infection or intracranial abscess and only patient 5 had severe neurological sequelae.

Recurrence of bleeding

Patient 4 had two episodes of bleeding. We found no such case in the English literature. In the first attack 2 hours after administration of parenteral vitamin K, we had to transfuse fresh frozen plasma because of oozing from the brachial vein. The bleeding stopped during the 1st hour of transfusion. He had not received vitamin K prophylaxis at birth but had self-correcting jaundice. About 70 days later he had an episode of intracranial bleeding which was also responsive to therapy. An episode of diarrhoea lasting 10 days and antibiotics for 3 days might impair intestinal flora and absorption of vitamin K. Between episodes of bleeding and during follow-up, all the coagulation factors were within normal limits. He experienced no further bleeding episodes in the 21-month follow-up period.

Galactosaemia and HDN

Although patient 8 had some other manifestations of the underlying disease such as jaundice and hepatomegaly, intracranial haemorrhage was the reason for admission. Galactosaemia must be considered in the differential diagnosis of jaundice in infants.[21–26] A deficiency of galactose-1-phosphate uridyl transferase results in accumulation of galactose-1-phosphate, which is thought to have a direct toxic effect on the liver. Diagnosis was delayed in our patient and she had not received vitamin K prophylaxis.

Recommendations for developing countries

To improve prophylaxis, the following must be considered. (i) At discharge of all births there should be a legal obligation to give parents a record containing information about vitamin K administration; (ii) there should be a well-baby check-up and centres must be obliged to record the data and administer vitamin K prophylaxis to any infant who has not previously received it; (iii) hospitals treating infants with HDN must be obliged to report these cases to local health departments and national registries; (iv) in addition to 1 mg vitamin K_1 for all babies after delivery, daily oral drops of combined vitamins D and K should be delivered freely in preventive care centres as soon as the preparation becomes available commercially.

Late HDN frequently presents with intracranial haemorrhage, leading to high mortality and morbidity. At the moment, different prophylactic strategies do not succeed in preventing all cases. Physicians must also be aware that late haemorrhagic disease can be the manifestation of an underlying disorder.

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