INTRACRANIAL HAEMORRHAGE DUE TO LATE HAEMORRHAGIC DISEASE OF INFANCY

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ABSTRACT

Thirteen cases of late haemorrhagic disease of infancy due to vitamin K deficiency presenting with intracranial haemorrhage were seen over a three – year period from 1984 to 1986. The clinical picture was fairly typical; a short history of being unwell (poor feeding, vomiting, irritability, high pitched cry, fits) and physical findings of pallor, a normal body temperature, impairment of consciousness, abnormal respiration and a very tense anterior fontanelle.

Vitamin K deficiency was implicated by the prolonged prothrombin time which rapidly returned to normal with vitamin K injection. The outcome was poor. Possible factors giving rise to vitamin K deficiency are discussed. The author suggests the introduction of the giving of vitamin K to all new-borns.

Key Words; intracranial haemorrhage, late haemorrhagic disease of infancy, vitamin K deficiency.

INTRODUCTION

Haemorrhagic disease of the newborn occurring in the first few days of life is well known. It's relationship to vitamin K deficiency has been well established. A similar bleeding tendency can occur beyond the first few days of life. In 1966, Goldman and Deposito[1] reported five cases, three of whom had intracranial haemorrhage, due to a bleeding tendency which responded to vitamin K administration. Since then, there have been many reports of a similar condition from various parts of the world.[2–15]

Various names had been given to this condition; hypoprothrombinemic bleeding in young infants, the haemorrhagic syndrome of early childhood,[2] late haemorrhagic disease of infancy,[3] vitamin K deficiency in infants beyond the neonatal period,[4] acquired prothrombin complex deficiency in infants[5,6] and delayed haemorrhagic disease of the newborn.[7] Its is suggested to call the entity late haemorrhagic disease of infancy (LHD). This comminaction deals with 13 cases of intracranial haemorrhage due to LHD, seen over a three – year period.

MATERIALS AND METHODS

Thirteen patients with LHD were seen in the Paediatric Unit of the Alor Setar General Hospital over a three year – period from 1984 to 1986. A detailed paediatric history and physical examination was recorded with particular emphasis on perinatal events, previous history of vitamin K administration, type of feeding (whether breast-fed, formula-fed or mixed) and history of antibiotic administration and diarrhoea during the two weeks preceding admission.

Intracranial haemorrhage (subarachnoid, subdural, intraparenchymal or intraventricular) was confirmed by cne or more of the following procedures which were done on the patients; lumbar puncture, subdural puncture, ventricular puncture and CT head scan. The size of the liver was noted by palpation and measured from the subcostal margin in the midclavicular line. The liver was considered to be enlarged when this measurement exceeded three centimetres.

The investigations that were done include; total blood cell counts, prothrombin time (PT), liver function tests and blood and cerebrospinal fluid bacterial cultures. The PT was done using the modified Quick's one-stage method. The reagent used was ORTHO Brain Thromboplastin and the control used was ORTHO Plasma Coagulation Control (from Ortho Diagnostic Systems Inc.). The PT was done before and after vitamin K administration. Vitamin K deficiency was deduced by the prolonged PT which was rapidly corrected with vitamin K injection. We did not do the partial thromboplastin time and specific coagulation factor assay for reasons of cost and unavailability of such tests in the hospital.

The treatment of the patients consisted of; blood transfusion for anaemia,intravenous vitamin K (ranging from one to five mg per dose), measures to reduce increased intracranial pressure (fluid restriction to two-thirds maintenance requirements after initial resuscitation, use of mannitol, dexame thasone and frusemide and mechanical hyperventilation) and anticonvulsants (phenobarbitone and / or phenytoin sodium) to control fits.

RESULTS

The clinical data is summrised in Table one. There were 12 ethnic Malays and one ethnic Siamese. There were 11 males and two females. Their ages range from 14 to 52 days. All of this were fullterm babies with an uneventful birth history. Nine of the babies were delivered at home, three in the hospital and one in a private maternity home. None of the babies were given vitamin K at birth and all of them were exclusively breast-fed. There was no history of trauma and no family history of a bleeding tendency. Only one of the babies was given an oral antibiotic (ampicillin) for five days prior to admission.

The patients had one or more of the following symptoms; low grade fever, poor feeding, vomiting, irritability, high pitched cry, diarrhoea, fits, jaundice, cyanotic attacks and a bleeding manifestation. The symptoms developed suddenly in a previously well baby and were of short duration, usually for a day or two before admission. Only two patients had diarrhoea; the diarrhoea was mild and the duration was one to two days.

The main findings on admission were pallor, impairement of consciousness (varying from irritability to drowsiness to deep coma), abnormal respiration (either slow irregular respiration with occasional gasps or tachypnoea) and a very tense anterior fontanelle. Fits were seen either before or after admission in 11 of the 13 patients. The fits were variable; it was either tonic and/or clonic and the distribution was focal, multifocal, unilateral or generalised. Although fever was a frequent complaint (9 of 13 patients), all the patients were afebrile on admission when the axillary temperature was taken. This could be explained by the fact that fever could mean an unwell baby rather than actually having a raised body temperature in Malay culture. Jaundice was present in six patients and it was mainly unconjugated hyperbilirubinemia. The liver was significantly enlarged in only two patients on admission.

The laboratory data is summarised in Table II. The total blood white cell counts were normal. However, thrombocytosis was a frequent finding. This was especially so when the blood platelet counts were repeated later during the patient's hospital stay. The serum aspartate aminotransferase level,which was done on three patients was normal. The PT, which was done on 10 patients on admission, was pro-

Table 1: Clinical data of 13 patients with intracranial haemorrhage due to late haemorrhagic disease of infancy.

Patient	Ethnic group	Sex	Age on admission (days)	Antibiotics before admission	Main symptoms	Main clinical findings on admission	Outcome
1.	Malay	M	45	none	jaundice 5 days, poor feeding 1 day.	afebrile, drowsy, pallor jaundice, fits, tachypnoea, tense AF. Liver 1 cm.	died
2.	Malay	F	44	none	fever and poor feeding 2 days.	afebrile, pallor, drowsy, irregular respiration with gasps, tense AF. Ecchymoses of trunk, liver 2 cm.	alive
3.	Malay	M	44	none	fever and fits 1 day.	afebrile, pallor, deep coma, irregular respiration with gasps, tense AF. Liver 2 cm.	died
4.	Malaya	M	36	none	apnoeic spells and cyanotic attacks 1 day.	afebrile, pallor, drowsy jaundice, fits, tense AF Liver 2 cm.	alive
5.	Malay	M	48	none	fever, vomiting, diarrhoea, jaundice and fits 2 days.	afebrile, pallor, deep coma, jaundice tense AF. Liver 1 cm.	died
6.	Siamese	M	33	yes	fever, poor feeding, vomiting, diarrhoea, fits 1 day	afebrile, pallor, coma, jaundice, irregular respiration with gasps, tense AF. Liver 1 cm.	alive
7.	Malay	M	22	none	fever, poor fedding, vomiting, irritable, jaundice, abdominal distension 1 day.	afebrile, pallor, jaundice, high pitched cry, fits, tense AF. Bleeding from nostril, puncture sites. Liver 2 cm.	alive
8.	Malay	M	30	none	fever, poor feeding, jaundice, fits and bleeding from ear 1 day.	afebrile, pallor, coma, jaundice, irregular respiration, tense AF. Liver 4 cm.	died
9.	Malay	F	49	none	fever, cough 3 days, poor feeding, vomiting, high pitched cry, fits 1 day.	afebrile, pallor, deep coma, irregular respiration with gaps, tense AF.	died
10.	Malay	M	32	none	irritable, fits 1 day	afebrile, drowsy, pallor tense AF. Liver 2 cm.	alive
11.	Malay	M	14	none	fever, poor feeding, vomiting, bleeding from umbilicus 1 day.	afebrile, pallor, irritable, tachypnoea, tense AF. Bleeding from umbilicus. Liver 2 cm.	alive
12.	Malay	M	40	none	fever, poor fedding, vomiting, irritable, fits 1 day.	afebrile, pallor, irritable, tachypnoea, tense AF. Liver 1 cm.	alive
13	Malay	M	52	none	poor feeding, vomiting, fits 1 day.	afebrile, pallor, deep coma, irregular respiration with gasps, tense AF. Liver 3 cm.	died

Note: M – Male ; F – Female; AF – anterior fontanelle.

Table 11: Laboratory data of 13 patients with intracranial haemorrhagic due to late haemorrhagic disease of infancy.

Patient	Haemoglobin (g/dl)	Total white cell count (per mm^3)	Platelet count (per mm^3)	Serum bilirubin (mg/dl)	AST (IU/l)	PT (s) before vitamin K	PT (s) after vitamin K
1.	ND	ND	ND	9.6 D=0.6	ND	ND	ND
2.	5.2	18 400	350 000	2.6 D=0.6	ND	> 120 C=15	15 C=15
3.	4.4	6 700	ND	ND	ND	ND	ND
4.	5.0	16 700	470 000	9.4 D=0.6	ND	ND	ND
5.	ND	ND	ND	ND	116	> 120 C=15	ND
6.	5.2	10 900	800 000	ND	39	120 C=15	16 C=15
7.	9.2	ND	180 000	9.3 D=0.6	ND	> 120 C=14	15 C=14
8.	6.9	11 000	300 000	10.8 D=0.9	ND	> 120 C=15	18 C=14
9.	6.1	20 000	450 000	ND	ND	23 C=14	15 C=14
10.	6.4	14 100	290 000	ND	ND	27 C=14	15 C=14
11.	8.0	20 000	650 000	8.6 D=2.5	ND	> 120 C=14	17 C=14
12.	5.1	16 700	270 000	ND	ND	> 120 C=15	15 C=15
13.	5.1	10 000	440 000	1.8 D=0.6	80	52 C=15	14 C=15

Note: AST – asparatate aminotransferase ; D – conjugated bilirubin level ; PT – prothrombin time ; > – more than ; ND – not done or result cannot be traced, C – control

longed. The PT returned to normal after vitamin K injection. The amount of vitamin K given to each patient varied from three to 15 mg; the drug was not necessarily given in a single dose. The time taken for the PT to return to normal range from six to 48 hours. Blood and cerebrospinal fluid cultures for aerobic bacteria did not show any growth.

Intracranial haemorrhage was present at one or more of the following sites; subarachnoid , subdural, intraparenchymal or intraventricular space. The most frequent site was the subarachnoid space (12 of 13 patients). This was frequently associated with subdural bleeding. The CT head scan of one patient (case 11) with intracerebellar and intraventricular haemorrhage is shown in Figures one and II. An associated bleeding manifestation was present in five patients; this was either skin ecchymoses or bleeding from the umbilicus, ear, nose, intravenous drip site, injection site or lumbar puncture site. The mortality rate was 46% (six out of 13 patients).

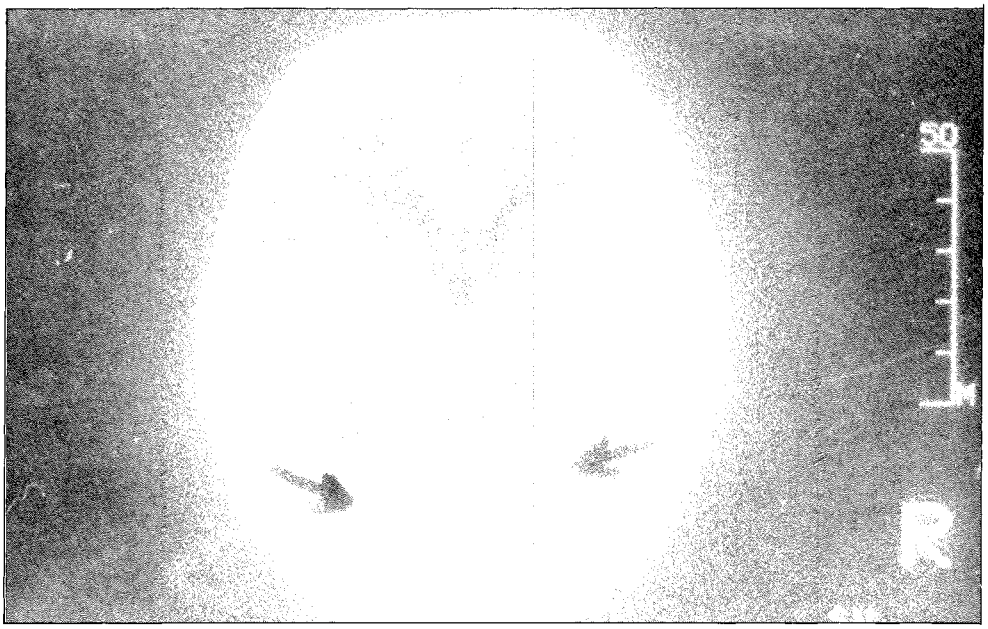

Fig. I: The CT head scan of one patient showing haemorrhage into the occipital horns of the lateral ventricles (indicated by arrows).

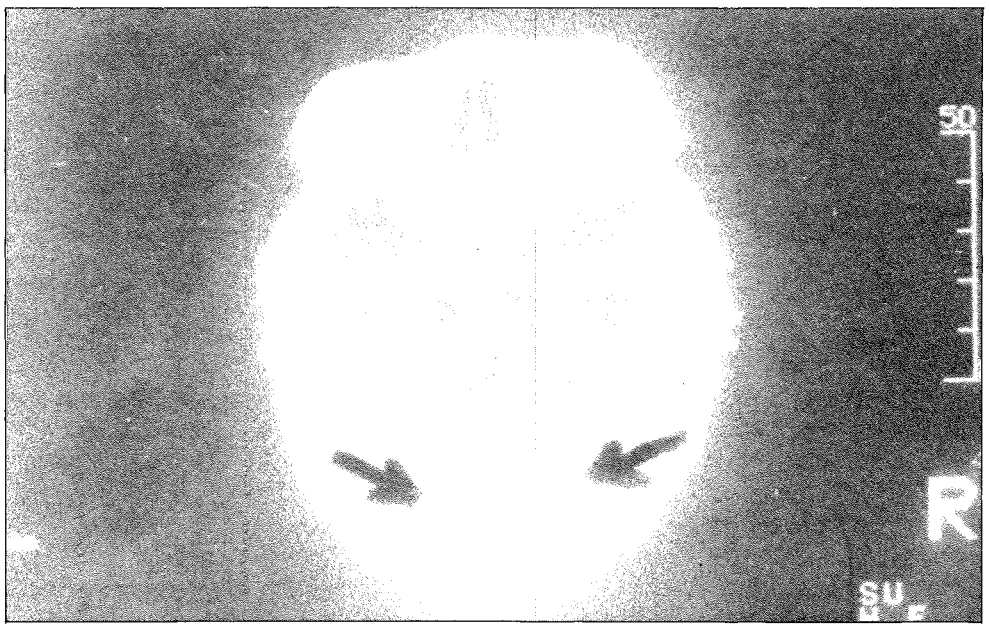

Fig. II: The CT head scan of the same patient showing bilateral intracerebellar haemorrhage; more extensive on the right side (indicated by arrows).

DISCUSSION

The commonest mode of presentation of LHD is intracranial haemorrhage.[1,3,4,5,12,13,14] This can either be subarachnoid, subdural, epidural, intracerebral, intracerebellar or intraventricular. Frequently, more than one intracranial site are involved. The commonest is subarachnoid haemorrhage frequently associated with subdural haemorrhage.[14] Other forms of presentation are skin ecchymoses, nodular purpura,[16] bleeding from the umbilicus , gastrointestinal tract, nose, ear, venepuncture site and lumbar puncture site. Bleeding manifestations from more than one site can occur in the same patient. The bleeding manifestations occur spontaneously in the absence of trauma.

It is useful to divide LHD into two broad groups; the idicpathic group and the secondary group.[17] Secondary LHD can be due to prolonged diarrhoea, malabsorption (as in cystic fibrosis, biliary atresia, $\pounds_1$ – antitrypsin deficiency, hepatitis, abetalipoproteinemia and coeliac disease) or chronic warfarin exposure. In both groups, the common factor is vitamin K deficiency. While secondary LHD can occur at any time in the first year of life, idiopathic LHD usually occur between one and three months of age with a peak in the second month. Our small series of patients belong to this group. Idiopathic LHD has several characteristic features;[14] it is more common in Oriental babies (as frequently reported in Thailand, Japan and Taiwan); it usually presents in the second month of life; intracranial haemorrhage is the usual mode of presentation; babies are usually breast-fed and it is more common in males. Our series were consistent with the above features.

Vitamin K deficiency is the underlying cause, as evidenced by the fact that the PT rapidly returns to normal after it's administration. Several reasons have been cited for the vitamin K deficiency in these infants; breast-feeding, the practise of not giving vitamin K to all newborns at birth in the last few years, the use of antibiotics and diarrhoea.

The newborn baby does not have excess vitamin K; rather some are deficient at birth. Using high performance liquid chromatography, Shearer et al[18] found that vitamin K was undetectable in the cord blood of nine term infants despite levels of 0.13 to 0.19 mg/ml in their mothers. When six mothers were given vitamin K intravenously, their vitamin K blood levels rose to between 45 and 93 mg/ml. However, the vitamin K levels in the cord blood of their infants range from undetectable to only 0.14 mg/ml.

After birth, the only important source of vitamin K is the diet. Fat-soluble vitamin K_1 or phylloquinone is the main from of vitamin K in plants and vegetable oils. Human milk contains only small amounts of vitamin K_1; it is usually less than 20mg/l and frequently less than 5mg/l. Commercial milk formulas contain more than 50mg/l of vitamin K_1. It has been shown that haemorrhagic disease of the newborn is more common in breast-fed than formula-fed babies in the absence of vitamin K supplementation at birth.[20] Isarangkura et al[21] showed that the vitamin K levels of maternal breast milk of infants with LHD were much lower than in controls.

Shirahato et al[22], using Normotest for vitamin K-dependent coagulation factors, found lower values in breast-fed babies than those on mixed feeding at one month of age. However, Jiminez et al[23] found no significant difference between breast-fed and formula-fed babies at one month of age; these babies had been given vitamin K at birth. His study was criticized because of the small numbers of infants involved and the statistical methods used in the analysis.[24]

Many species of bacteria produce vitamin K in the colon. The vitamin K is absorbed in the colon too.[25] The bacterial content in the colon of breast-fed babies differ from those formula-fed. The predominant bacteria in breast-fed babies is gram-positive bacilli especially **Lactobacillus bifidus. L. bifidus** has not been studied but a related species **L. casei** does not produce vitamin K_2. It could be that the vitamin K produced in the colon is less in breast-fed infants than formula-fed ones.

Antibiotics, especially the broad-spectrum ones, cause alteration of the bacterial flora in the gut and reduces the population of vitamin K-producing bacteria. Diarrhoea too, especially when prolonged, produces a similar effect.[27,28] The absorption of vitamin K may be different in infants as compared to older children or adults. Komazawa[29] showed that orally administered vitamin K is less well absorbed in infants compared to adults. It is highly probable that a combination of factors (low vitamin K level at birth, supplemental vitamin K not given at birth, breast-feeding, preceding antibiotics, preceding diarrhoea) are responsible for vitamin K deficiency in idiopathic LHD.

It is not known why the bleeding tendency manifests itself at the second month of life and why intracanial haemorrhage is the commonest mode of presentation. It could be that the vitamin K level is at it's lowest during this period. As for the intracranial haemorrhage rapid brain development with rapid changes in surrounding supportive tissues and blood vessels during this period could play a role.[12] Further studies are needed in these areas.

Significant mortality and morbidity can result from the intracranial haemorrhage. In Bhanchet's[5] series, of those with intracranial haemorrhage, the mortality rate was 50%. In Motohara's[30] series of 10 patients, 3 died. In Chaou's[14] series of 32 patients in Taiwan, the mortality rate was 9.4%. In our series of 13 patients, the mortality rate was 46%. We have not analysed the morbidity of our patients. However, in Motohara's series, of 7 patients who were discharged; three were well, 2 had cerebral palsy and one had hydrocephalus. In Chaou's series, 29 patients were followed up for 2 to 18 months; only one was normal, the remainder had the following problems: mild to moderate developmental delay, microcephaly, cerebral palsy, severe psychomotor retardation and epilepsy.

There is reason to believe that idiopathic LHD may be not uncommon in Malaysia and that it is often not diagnosed. Carefully olanned studies should be started to find out the extend of the problem and measures that need to be taken to prevent it. Until further evidence to show what vitamin K does not prevent haemorrhagic disease (whether early , classical or late type), it is suggested that the policy of giving vitamin K to all newborns be started, particularly to those who are to be breast-fed, irrespective of their birth weights and perinatal problems. In fact, the American Academy of Paediatrics recommend that all newborns be given vitamin K at birth.[31] Oral vitamin K[32,33] could be a useful alternative to parenteral vitamin K, especially where a large number of our babies are delivered at home. Supplementary vitamin K could be given to our breast-fed babies at about a month of age to boost their level of vitamin K. Studies on the effectiveness of oral and parenteral vitamin K in the prevention of idiopathic LHD are in progress in Japan and Taiwan.

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