

SEVERE HYPOPROTHROMBINAEMIC BLEEDING IN THE BREAST FED YOUNG INFANTS

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Hypoprothrombinaemic bleeding in the newborn infant or haemorrhagic disease of the newborn, particularly during the first week of life was well known and widely documented. The aetiology of haemorrhagic disease of the newborn was obscure until 1937 when Brinkhous et al first demonstrated the existence of a decrease prothrombin content in the newborn infant. Later on, it was realised that a transitory deficiency in proconvertin or Factor VII was an important factor in its aetiology (Loeliger and Koller 1952; Douglas and Davies 1955; Dyggve 1958). A decrease level of Stuart Prower factor was found in the blood of newborn premature infants by Schulz and Creveld and they also found a marked decrease in this factor in a case of haemorrhagic disease of newborn (Creveld 1959).

Although hypoprothrombinaemic bleeding in young infants after the second week of life was not common when compared to the newborn infants, yet it was not unknown especially those cases following diarrhoea diseases and treatment with antimicrobial agents (Goldman and Deposito 1966), liver diseases such as biliary atresia and the ingestion of salicylates or coumarin derivatives by the infant or lactating mother.

This paper describes a group of apparently healthy, young, full term infants who developed severe haemorrhage associated with prolonged coagulation time and prothrombin time, and who were not suffering from diarrhoea diseases, liver diseases and had not ingested any antimicrobial agents or salicylates before the onset of the bleeding episode.

MATERIAL

23 babies were admitted into the Paediatric Unit, General Hospital, Singapore, during a 5-year period because of severe bleeding and anaemia. Their ages ranged from 21 days to 60 days with a mean of 37 days. Figure 1 showed the age incidence of the affected babies and also revealed that the majority, about 83%, were between 21-49 days. They were all full term babies with a normal history at labour. The sex distribution (Fig. 2) was not statistically

significant. The numbers of affected babies living in the rural area were slightly more than those living in the city (Fig. 3).

All the 23 affected infants were Chinese, although the records on admission of all other patients into the Unit for one year period showed that of the 6,954 patients admitted 75% were Chinese, 14% Malays, 9% Indians and 2% Eurasians and Europeans (Fig. 4). The fact that only Chinese infants are affected is interesting, the significance of which will be discussed later on.

Figure 5 showed the presenting clinical features on admission. All the infants had tense fontanelle and pallor on admission and so it was not surprising that many were admitted as cases of meningitis from the admission room. 87% of the patients had a history of vomiting 1-3 days before admission. Many patients (61%) were admitted in coma which varied from drowsiness to coma IV. Haemorrhage which could be detected by simple clinical examination was seen in 48%, although it would be shown later that all the affected babies had intracranial haemorrhage. One third of them had gastrointestinal bleeding as manifested by blood stain or coffee ground colour vomitus and melaenic stools. One third presented with ecchymosis or bleeding under the skin and the rest had bleeding in the mouth, gums and palate. Fever was present in 43% of the patients. Convulsion, either prior to or on admission was not very common accounting for 39% of the cases. The convulsion varied from twitching of one side of the body, particularly the limbs to generalised clonic and tonic movement of all the limbs. The pupils were dilated and non-reactive to light in 9 cases (39%), two thirds of them had unilateral and one third had bilateral dilatation. Unilateral ptosis were present in 3 patients (13%). All these 3 cases had the subdural haematoma over the same side of the ptosis. Only one patient presented with cyanotic attack on admission.

The haematological findings (Table I) showed that all the patients had a low haemoglobin level, with a mean of 6.6 Gm%. The clotting

AGE INCIDENCE

RANGES FROM 21 days to 60 days

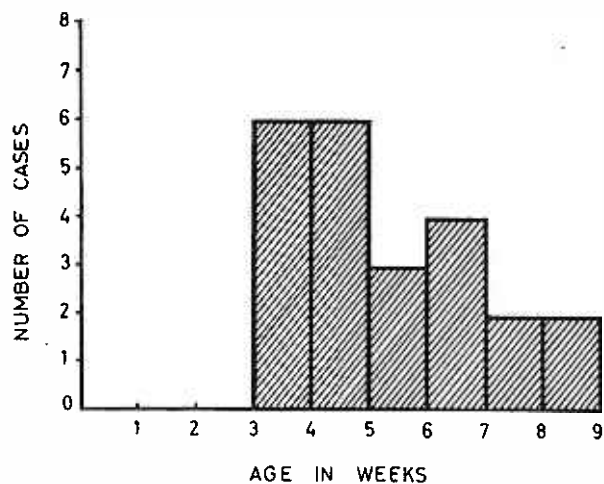


Fig. 1.

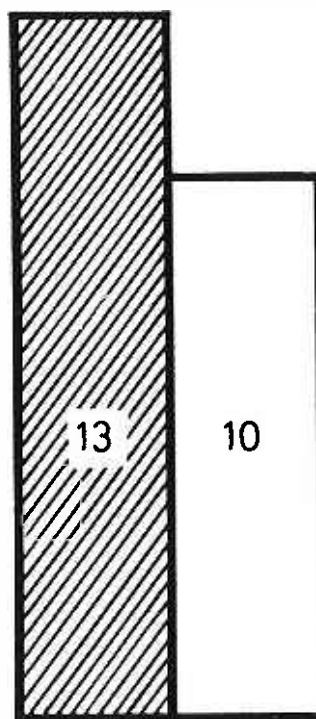
RESIDENCERURAL CITY

Fig. 3.

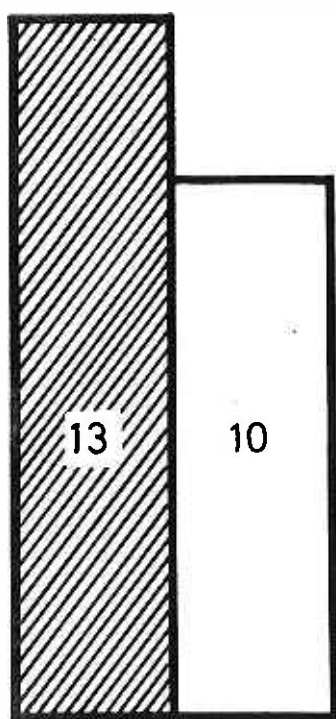
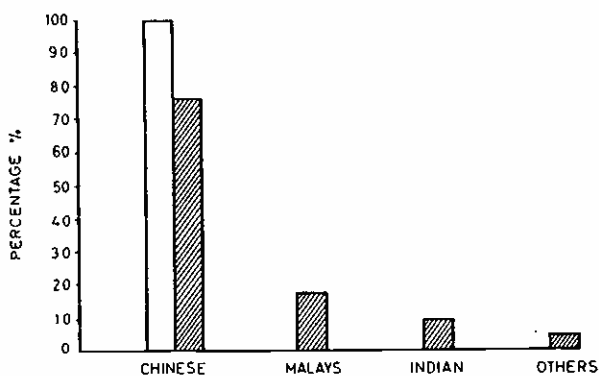
SEX DISTRIBUTIONMALE FEMALE

Fig. 2.

RACIAL DISTRIBUTION

□ Patients with prolong prothrombin time.
 ▨ Patients admitted to Paediatric Unit for 1 year period.

Fig. 4.

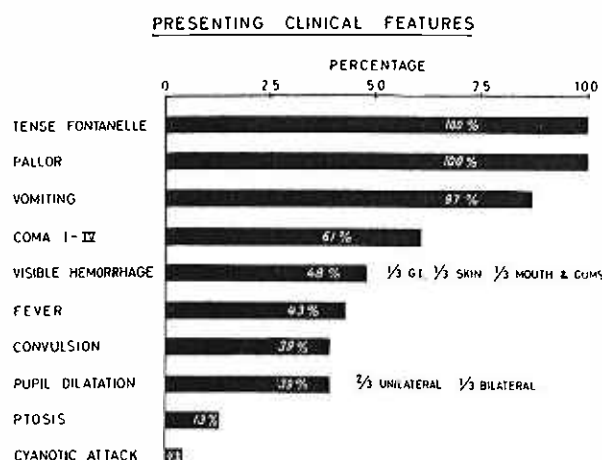


Fig. 5.

time was prolonged and the prothrombin time varied from 24 seconds to 90 seconds with a mean of 47 seconds. The plasma fibrinogen was done in 2 cases and both showed levels within the normal limit. The platelets were not low.

TABLE I

HAEMATOLOGICAL FINDINGS

Hb range from	3.4 Gm % to 10.2 Gm % (mean 6.6 Gm %)
T.W. range from	11,100-45,000/c.mm.
Platelets range from	190,000-560,000/c.mm.
Clotting time range from	8 min.-20 min. +
Prothrombin time range from	24 sec.-90 sec. (mean 47 sec.)
Plasma fibrinogen	0.28 Gm % and 0.58 Gm %

Subdural haematoma were elicited in 21 patients, 2 of whom had bilateral haematoma. Of the 13 patients who succumbed, all were found to have subdural haematoma at post mortem. In 9 of the cases, the haematoma were found by subdural tap. 3 cases had their subdural haematoma drained at operation. In the remaining 2 patients where subdural haematoma were not elicited by subdural tapping, subarachnoid haemorrhage was present at lumbar puncture. Both these patients were still alive and were not operated on. One was a spastic diplegia, whilst the other one had no physical sequelae. Lumbar puncture was done on only 12 patients, and all revealed evenly blood stained fluid suggestive of subarachnoid haemorrhage. 19 cases were investigated for fracture of the skull, 13 at post mortem and

6 radiologically. None of them showed any evidence of fracture.

A detail history of the affected infants' diet and medication prior to their illnesses revealed that all the infants were breast fed (Table II) and that 80% of them took "Gripe Water".

TABLE II

BABIES' DIET & MEDICATION PRIOR TO ILLNESS

Breast Milk	100 %
"Gripe Water"	80 %
Keng Fong San	20 %

The amount taken varied from 1 teaspoon a day to 1 teaspoon 3 times a day. Most of the infants were given this "Gripe Water" after the second week of life. The constituent of "Gripe Water" as reproduced from the bottle label was shown in Table III. It is interesting

TABLE III

COMPOSITION OF GRIPE WATER

Ol. Anethi	0.10 c.c.
Sod. Bicarb.	1.00 gram
Alcohol Dehyd.	4.96 c.c.
Syrup	29.36 c.c.
Aqua ad.	100.00 c.c.

to note that it contained 4.96 c.c. of alcohol dehydrate per 100 c.c. of solution. "Keng Fong San" is a local concoction of Chinese medicinal powder which on analysis showed presence of small amount of Phenacetin, Mercuric Sulphide and various unknown Chinese herbal products. It had been used very extensively among the local Chinese for all sorts of complaints varying from simple fright to convulsion and fever. Among the affected infants, only 20% had received this powder off and on prior to their illnesses for the prevention of 'fright' to using it for no apparent reason except that the old folks at home said that it was good for the baby.

The diets of the mothers of these affected infants are also interesting. All the mothers had taken alcohol prior to their babies' illnesses. The type of alcohol consumed varied from 'tonic' wine such as 'Wincarnis', 'D.O.M.' or 'Sevarello', to brandy and Chinese rice wine. The amount taken again varied from approximately 6-8 drachm twice a day to three times

a day. The time when these mothers began taking the alcohol varied from 6 days to 12 days after birth. During the first 4-6 weeks after labour, besides consuming alcohol, they also took a diet consisted mainly of rice, sesame oil, ginger, chicken and lean pork. Fresh vegetables and fresh fruits were not taken.

The treatment of these patients consisted of intramuscular Vitamin K injection 5 mgm and blood transfusion. The prolonged coagulation time and prothrombin time which were found on admission returned to normal 8 to 16 hours after the Vitamin K injection and blood transfusion. Subdural tap was done after the prothrombin time had become normal. 5 cases were submitted to surgery mainly for the removal of the membrane after several weeks of subdural tapping. 4 cases were alive and had no physical sequelae, one infant died soon after the operation.

Of the 23 patients described in this paper, 10 patients were alive and 13 died. Table IV

TABLE IV
RESULT

Alive	10 cases
Normal	7 "
Physical sequelae	3 "
Deaths	13 cases
Within 12 hours	6 "
Within 24 hours	5 "
Within 36 hours	2 "

showed that all the 13 cases died soon after admission, 6 cases within 12 hours, 5 cases within 24 hours and 2 cases within 36 hours after admission. Follow-up of the 10 patients who were alive by the author revealed that 7 patients developed normally and had no physical sequelae. Of the 3 patients who developed sequelae, one was a spastic diplegia with microcephaly, one had a right spastic hemiparesis and another acquired a left spastic monoplegia involving the upper limb. The mental development of the latter 2 patients was satisfactory.

DISCUSSION

This discussion will be devoted mainly to attempting to explain the reason for the severe hypoprothrombinaemic bleeding in this group of apparently healthy young infants. Bleeding from known causes such as biliary

atresia, prolonged gastro-enteritis or antibiotic therapy and ingestion of salicylates are not included.

Fresh et al (1957) studied the blood prothrombin, proconvertin and proaccelerin in normal infancy and found that not only were the level of prothrombin and proconvertin low during the first 3 days of life, but it also showed a secondary dip at some time in the second and sixth week. Brinkhous et al (1937) reported that the prothrombin level of infants of two months old was about 60% of normal adults and thereafter rose slowly to 100% at the end of 1 year. Plum (1949) mentioned that during the second half of the first month of life, the prothrombin is lower than that of the adult and during the second and third month, the distribution was approaching the normal adult level. Although these authors in their study of normal and healthy infants demonstrated that the prothrombin level during the post neonatal period was still lower than that of older children and adults yet severe hypoprothrombinaemic bleeding in this age group was not seen and as far as I know had not been described in healthy infants. Fresh et al (1957) suggested that the excess proaccelerin compensates for the deficiency of the other 2 factors, viz. prothrombin and proconvertin in preventing the normal infant from developing any bleeding condition.

The group of infants described in this paper had several significant facts in common, viz. all of them were breast fed; the nursing mother consumed alcohol daily during the period prior to their illnesses; their ages were within the 3rd week to 9th week of life; and they were all Chinese.

Analysis of the feeding history of 1,317 infants within the first three months of life, who were admitted into the Unit, revealed that 36% were breast fed, 10% had a mixed feeding of breast milk and cow's milk and 54% were on a cow's milk formula. Thus the fact that 100% of these infants with hypoprothrombinaemic bleeding were breast fed is significant. Since various authors had shown that breast fed infants are susceptible to hypoprothrombinaemic bleeding, it is possible that breast feeding among this group of affected infants is the predisposing factor to their hypoprothrombinaemic bleeding. Dam and his associates (1952) showed that depression of prothrombin was confined to breast fed infants who had not received Vitamin K or whose mother had received no Vitamin K. He also showed much

lower values of Vitamin K in human milk than in cow's milk when assayed in Vitamin K deficient chicks. Sutherland et al (1967) in a study of 3,338 full term newborn had shown that the increase bleeding associated with hypoprothrombinaemia was confined to breast fed infants who did not received Vitamin K. This hypoprothrombinaemia was associated with severe depression of all the Vitamin K dependent factors. They further mentioned that Vitamin K offers little advantage to infants fed on cow's milk, but breast fed infants who did not receive the Vitamin K had a 5% increase risk of bleeding. In a few cases it was demonstrated that these coagulation disturbances and bleeding responded to cow's milk. They concluded that breast feeding is a necessary prerequisite to Vitamin K deficient haemorrhagic disease of newborn. Gellis and Lyon (1941)) in a study on newborn infants found that the group of infants fed at the breast every four hours, beginning twelve hours after birth showed the greatest decline in their prothrombin indices and the most prolonged recovery to initial levels. Whereas the group of infants who received additional feedings of cow's milk after each nursing, beginning twelve hours after birth, showed the least decline in prothrombin indices and the most rapid recovery to normal values. Salmononsen and Nygaard (1939) also showed that infants on a mixture of breast milk and cow's milk did not develop low prothrombin levels characteristic of infants who received breast milk only. Sanford et al (1932) mentioned that they had not seen a single case of haemorrhagic disease of newborn for a 2-year period amongst infants who were on a cow's milk formula from 4 hours after birth onwards.

Among the various drugs which are secreted in the breast milk, alcohol is one of them (Catzel 1966). All the infants in this series apparently had been consuming alcohol daily from the breast milk as all their nursing mothers had been taking alcohol daily for periods varying from 2 weeks to 6 weeks prior to their bleeding episodes. Alcohol metabolism is concentrated in the liver and chronic alcoholism can result in hepatic lesion leading to a depression of prothrombin synthesis and increased bleeding tendency. Since the immature liver of the newborn does not have the same prothrombin forming capacity as the adult (Plum 1949) it is possible that these affected infants' livers had their prothrombin forming capacity depressed by the alcohol even though the period of consumption of alcohol

was only for several weeks. The "Gripe Water" which had been taken by 80% of these infants also contained a small amount of alcohol (Table III). The small amount of alcohol will not affect other infants but when given to these infants who were already consuming alcohol from their mothers' breast milk, it may be significant. Olwin (1954) described 2 patients where the use of alcohol caused deviation from the desired prothrombin time. Stormer and Kantsch (1954) mentioned one case where alcohol consumption resulted in a depression in Factor VII and produced bleeding tendency. Waris (1963) in a study of the effect of ethyl alcohol on some coagulation factors in men during anticoagulant therapy mentioned that in his experiment, alcohol did not seem to have a distinct influence on the Quick's thromboplastin time, although a minor tendency from the thromboplastin time to shorten was demonstrable. With the Owren's thrombotest method, a drop was observed in some cases leading to a lengthening of coagulation time. He concluded that for individuals who are on anticoagulant therapy, the incidental use of alcohol was alright, but caution must be taken because of individual variation.

The youngest of the affected infants was 21 days old and the oldest 60 days. This coincided with the period when the nursing mothers began to take alcohol. The majority of Chinese nursing mothers who consumed alcohol as a tonic, began taking it 7-10 days after delivery and took it daily after meals up to one month after labour. Very few began taking alcohol as early as the 3rd day and some continued taking it irregularly and in diminishing amount up to the end of the 2nd month. These cases were not seen after the 2nd month because after that period none of the nursing mothers consumed alcohol daily. The 10 infants who were alive were followed up by the author regularly, a few for as long as 4 years. The prolonged coagulation and prothrombin time of these infants returned to normal 8-16 hours after admission and had remained normal throughout the period of the follow-up at the out-patients clinic. None of these infants had a recurrence of their bleeding episode which may be related to the fact that by the time they were discharged from the hospital, they were all put on cow's milk formulae.

It is interesting to note that all the affected infants in this series are Chinese. Among the various races in Singapore, viz. the Chinese, Malays, Indians and Pakistanis, Eurasians and Europeans, the majority of the Chinese mothers restrict themselves to a special diet during the

first month after delivery of their babies. Their diet consists of chicken, lean pork, ginger, sesame oil and rice, occasionally liver and black beans are included. Rice wine is commonly used to cook the chicken. Alcohol in various forms, viz. 'tonic' wine and brandy were taken after meals. Fresh vegetables and fresh fruits were not taken by the majority. The Vitamin K content of these foods, besides liver which was only taken occasionally by some women, was probably very low. Food with high Vitamin K content such as Alfalfa, fresh vegetables, e.g. cabbage, cauliflower, spinach and soybeans (Heinz 1962) were not taken at all. On the other hand, the nursing mothers of other races such as the Malays, Indians and Pakistanis, do not have a restricted diet during the first month after delivery. They take the usual diet which they had been taking before the birth of their babies. The Malay nursing mothers whom I interviewed do not take alcohol during their confinement, whilst some Indians consume brandy soon after delivery, but they do not take it regularly for one whole month. This difference in dietary habit and consumption of alcohol among the different races probably explains why this hypoprothrombinaemic bleeding is confined to the Chinese infants as seen in this series.

The mortality among the affected infants described in this paper is high. One of the reasons was that many of the patients were brought to hospital during the late stages of their illnesses. This can be shown by the fact that 61% of them were admitted in coma. All the 13 deaths succumbed within 36 hours of admission, of which about 50% died during the first 12 hours. All the cases had intracranial haemorrhages either subdural or subarachnoid or both. This explained the fact that all the patients had tense fontanelle and were pale on admission.

No attempt was made to determine whether the hypoprothrombinaemic bleeding was due to a depression of prothrombin, Factor VII or Factor X. As Factor V is not Vitamin K dependent and since all these infants responded to Vitamin K injection, therefore Factor V is probably not involved. The plasma fibrinogen was done on 2 infants before treatment and they both showed normal values. Van Creveld (1959) in a study of the concentration of fibrinogen in the plasma of normal newborn, felt that hypofibrinogenaemia did not play a significant part in haemorrhagic disease of the

newborn infant. As stated before, the prolonged clotting and prothrombin time of all these affected infants returned to normal after the administration of Vitamin K and blood, and remained normal throughout the period of follow-up. All the babies who survived were put on cow's milk formula in hospital and after discharge.

In conclusion it is hypothesized that all these apparently normal, full term, healthy, young infants suffered from severe hypoprothrombinaemic bleeding because as breast fed infants their prothrombin and Factor VII level were already lower than that of their artificially fed counterparts (Gellis and Lyon; Sutherland et al; Salomonsen et al). Added to this was the ingestion of alcohol from the breast milk daily for several weeks. The alcohol acting on the immature liver of the young infant could depress the prothrombin forming capacity to the extent that bleeding occurs. The low Vitamin K content in the nursing mothers' restricted diet during the period of confinement may also play a part in the aetiology.

SUMMARY

23 full term, healthy, young infants whose ages ranged between 21-60 days were admitted for severe hypoprothrombinaemic bleeding. Their presenting clinical features and haematological findings were described. Apart from gastro-intestinal haemorrhage, skin bruises and bleeding from the mouth and gums, all the infants had intracranial haemorrhages. The hypoprothrombinaemic bleeding responded to Vitamin K injection and blood transfusion and did not recur.

All the infants were breast fed, their nursing mothers were on a restricted diet which was low in Vitamin K and had consumed alcohol daily for periods varying from 2 weeks to 6 weeks prior to their illnesses, and they were all Chinese. It is hypothesized that breast feeding was a predisposing factor, and that alcohol which the infants ingested from the breast milk for several weeks could depress the prothrombin forming capacity in the immature liver of the young. The low Vitamin K content in the nursing mothers' restricted diet may also play a part.

Articles pertaining to the depression of prothrombin and Factor VII levels in breast fed infants and the effect of alcohol on some coagulation factors were briefly mentioned.

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