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Can the Late Form of Vitamin K Deficiency be fully prevented by Prophylaxis ?

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Abstract

From our experience infants with the late form of Vitamin K deficiency bleeding the following statements can be made : This disease occurs predominantly in breast fed infants. There is a prevalence of males (1.6 to 1). Eighty percent were between 2 and 6 weeks old. Over 50% had intracranial bleeding. At the time of diagnosis risk factors known to cause Vitamin K deficiency were not evident. In order to detect the vitamin K deficiency, PIVKA-II (Protein-Induced Vitamin K deficiency) is available as well as Hepaplastin test. Hepaplastin tests were carried out. These tests revealed markedly reduced values. PIVKA-II was present in all examined samples. In 1986 the committee recommended Prophylactic administration of vitamin K to all full-term newborn in West Germany as well as in all Japan. Incidence of idiopathic cases has decreased about three quarters (from 16 to 4 out of 100,000 birth in Japan) during 10 years.

Introduction

Recently much attention has been paid to intracranial bleeding in infants resulting from vitamin K deficiency.

It was noted that in spite of prophylaxis with vitamin K administration intracranial hemorrhage still occurred especially in breast-fed infants. It has therefore been postulated that lack of vitamin K in mother's milk might predispose to neonatal intracranial haemorrhage. These new born infants show clinical features such as the following.

- (1) Almost all cases appear between 2 weeks and 2 months after birth, especially in breast-fed infants.
- (2) Intracranial bleeding appears suddenly.
- (3) Extremely low values of vitamin K dependent factors are proved.
- (4) These values are improved after administering vitamin K (1-2mg) either per os or intravenously.

In Japan as well as in West Germany, the Ministry of Health Welfare have organized a research committee on idiopathic vitamin K deficiency since 1980.

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Apart from the committee, the research group was founded between Japan and West Germany. The first symposium was held in Freiburg (1986), where Dam first discovered vitamin K.

There are four important aims of this study :

Firstly, to answer the question, how can we detect vitamin K deficiency,

Secondly, to find any difference between Japan and West Germany from the view points of clinical features and so on take out.

Thirdly, to discover whether vitamin K is transported through the placenta?

And fourthly, to find how we can prevent vitamin K deficiency in the perinatal period.

1. How can we detect vitamin K deficiency.

(Method) 128 cases of umbilical venous blood were studied.

1. Hepaplastin test

2. PIVKA-II

Hepaplastin test is a freeze drying test devised to measure and control the change of factors II (Prothrombin), VII (Proconvertin), and X (Stuart Prowere factor) i.e., vitamin K. PIVKA-II is a protein induced by vitamin K absence or an antagonist. It is a well-known fact that at the end of the prothrombin cycle, there is gamma-carboxylglutamic acid (GLA).

In the case of vitamin K deficiency, glutamin acid could not be converted to GLA, and it becomes abnormal prothrombin. This is called PIVKA-II, using Latax test, this was tested.

In West Germany, it was tested by Prothrombin time, and if it was under 15%, the VK treatment was necessary.

(Results)

Between PIVKA-II designated as X, and Hepaplastin test designated Y, there is an

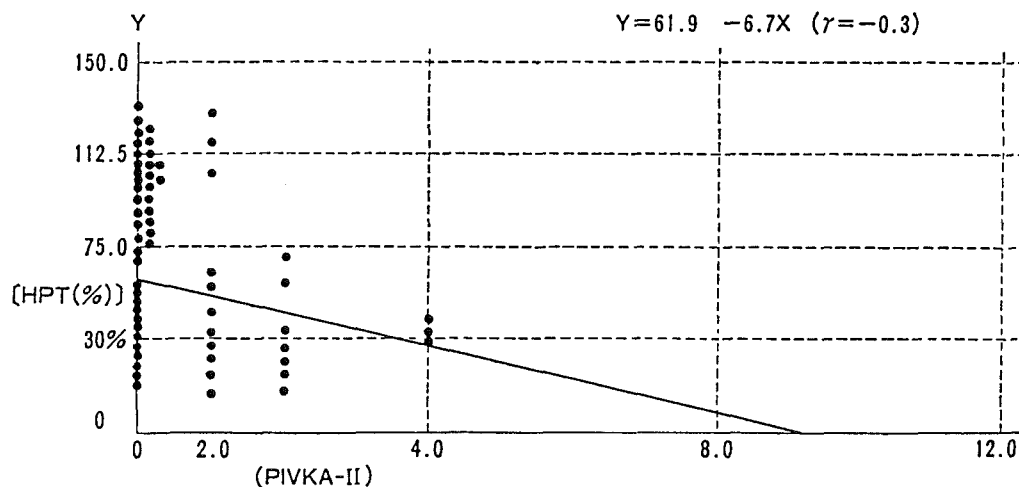


Fig. 1

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inversely proportional relation.

$$Y = 61.9 - 6.7X (r = -0.3)$$

The more PIVKA-II is detected, the less Hepaplastin test values are shown. If a Hepaplastin test under 30% is proven, we have to treat it as hypoprothrombinemia (Fig. 1).

2. Clinical symptoms of late form of VK deficiency

1. Feeding regimen

In Freiburg, 51 (91%) of the 57 infants were breast fed. The milk from the mothers of 4 patients was examined for its Vitamin K level. The results were in the low normal range (V. Kries et al., 1984).

Table 1 shows the types of feeding in Japan of which 476 cases (87.7%) were exclusively breast-fed. This percentage is markedly high compared to the average rate of breast feeding in Japan, which was estimated at about 50% during the survey period (Table 1).

Table 1. Methods of feeding of infants with vitamin K deficiency (from the second Survey of Japanese committee.)²⁾

	Idiopathic		Secondary		Near miss		Total	
	Cases	%	Cases	%	Cases	%	Cases	%
Number of cases	427	100	57	100	59	100	543	100
Breast feeding	387	90.6	38	66.6	51	86.4	476	87.7
Breast feeding mixed with formula	30	7.0	5	8.8	8	13.6	43	7.9
Prepared milk formula	4	0.9	9	15.8	0	0	13	2.4
Soybean formula	3	0.7	2	3.5	0	0	5	0.9
Unclear and others	3	0.7	3	5.3	0	0	6	1.1

2. Sex prevalence and season.

Sex prevalence : 36 of the 57 infants were male which results in a male predominance of 1.6 to 1. The patients' ages were between 1.1 and 23.6 weeks. 80% were between 3 and 7 weeks old. The average age was 5.2 weeks.

Season : It was remarkable that during the warmer season (April to September) almost twice as many infants fell ill.

Perinatal risk factors like prematurity or small-for-date babies, traumatic delivery, periparturient asphyxia were observed in 8 out of 57 (14%) infants. Infants with neonatal risk factors include 12 (21%) babies who had to be treated for prolonged icterus. Four infants showed failure to thrive. In 3 infants a positive BM-test pointed towards cystic fibrosis ; in 2 cases the diagnosis was confirmed afterwards. One child showed transitory bradycardia after delivery 3 infants had transient bleeding symptoms. Two infants had received drugs which are potential causes of Vitamin K deficiency, like antibiotics and anticonvulsants.

3. Regional feature

The occurrence of idiopathic type of Vitamin-K-deficiency was compared by regions ; as

shown Japan is a long of chain islands running from north to south ; Hokkaido is Japan's northernmost island and the occurrence of idiopathic Vitamin K deficiency there is the lowest. Tokyo is included in the central Kanto region, where the annual occurrence is 4.9 per 100,000 births. In Okinawa, the southernmost island of Japan, the occurrence was the highest (Fig. 2).

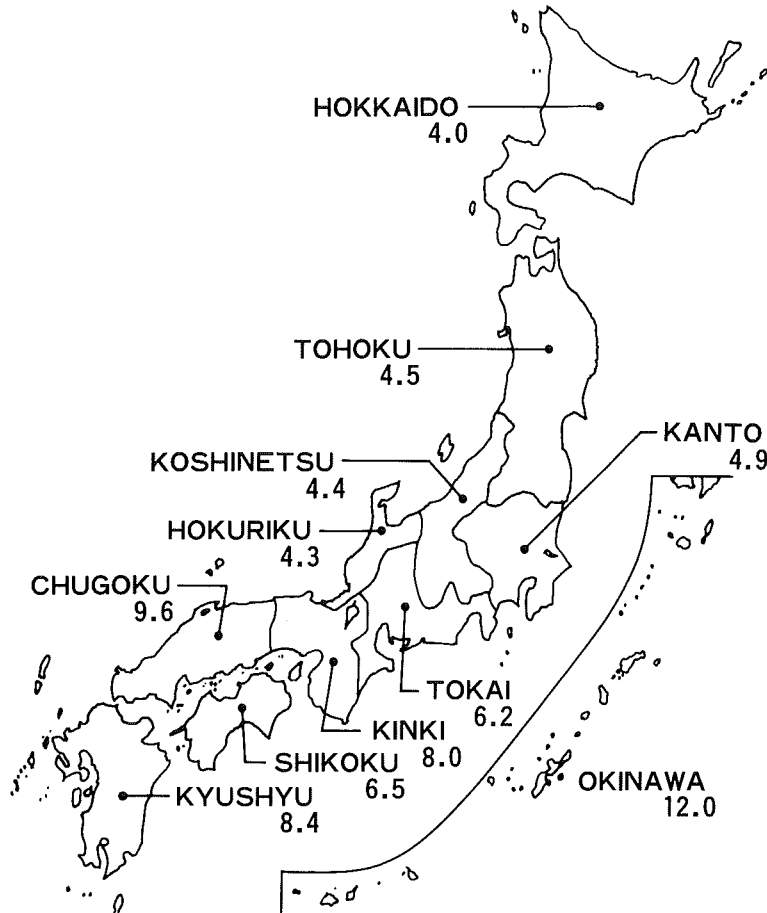


Fig. 2 Reported cases of idiopathic vitamin K deficiency in infancy per 100000 annual births in various regions of Japan

4. Symptoms and clinical findings.

Before bleeding became manifest the infants had unspecific symptoms like vomiting (34%), diarrhoea (11%), poor appetite (27%), restlessness (23%) and pallor (14%) (Fig.3). In those babies who afterwards were found to have CNS bleeding, marked somnolence (13%), sensitiveness to touch (9%) and painful moaning (14%) was noticed.

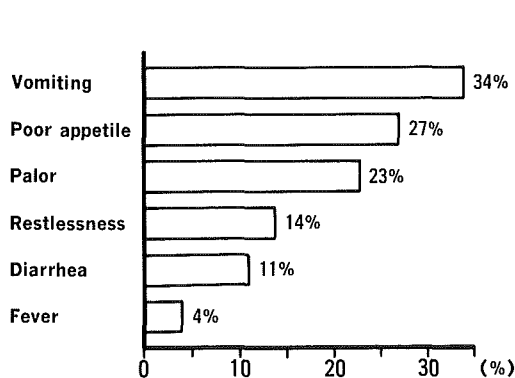


Fig. 3 Late form of Vitamin K-deficiency -bleeding Symptoms before bleeding

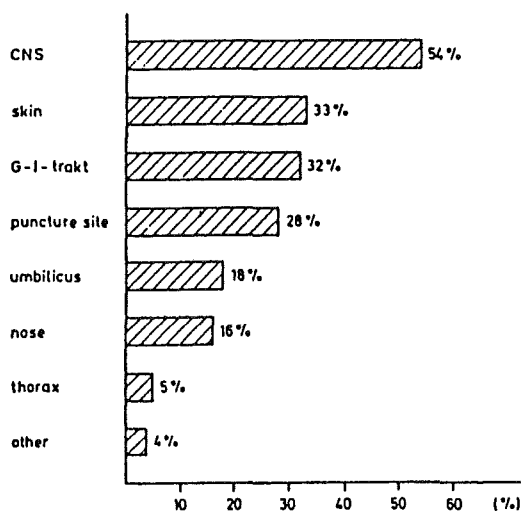


Fig. 4 Late of Vitamin-K-deficiency-bleeding Localisation of Bleeding

CLINICAL FINDINGS

The severity of the bleeding is shown by the fact that more than half of the patients (54%) had intracranial bleeding. The overall lethality was 23%. One third of the infants had bleeding into the skin or from the gastro-intestinal tract. One sixth of the patients had nose bleeding or omphalorrhagia (bleeding from the umbilicus). Bleeding secondary to puncture sites was observed in 28% of the patients. In 3 children (5%) a haematothorax was diagnosed. One child had bleeding from a torn frenulum of the tongue, another, one had a retro-auricular haematoma.

CNS bleeding in most cases occurred unexpectedly, since premonitory symptoms were completely absent or were so discrete, for instance in form of a minimal haematoma, that they were recognized as such only in retrospect. Six of the patients with CNS bleeding were comatose on admission. Two children were somnolent. Six infants had cerebral convulsions. In 13 patients the fontanel was bulging. Four children had opisthotonus. In 2 patients paresis of the facial nerve was present, one of them in combination with hemiparesis.

3. Is vitamin K transported through Placenta. ?

Van Creveld¹⁵⁾ and his group administered vitamin K to more than 10,000 mothers and reported that the frequency of neonatal bleeding (neonatal malaena) did not change. This study concluded that vitamin K does not pass through the placenta. However, according to the report of Shearer and others, vitamin K at the end of pregnancy is present in a very small concentration such that the amount can hardly be detected (table 2). They also reported that a very small amount of vitamin K (an average of 0.12 ng/ml) was detected in umbilical venous blood after they had given an infusion of vitamin K to the mother about one hour before

Table 2. Concentration of Vk_1 in the maternal and cord venous blood (SHEARER). (Vk_1 = vitamin K_1)

Subject no.	Plasma vitamin K_1 (ng/ml)	
	Maternal	Cord
1	0.29	n.d.
2	0.14	n.d.
3	0.14	n.d.
4	0.17	n.d.
5	n.d.	n.d.
6	0.21	n.d.
7	0.13	n.d.
8	0.26	n.d.
9	0.27	n.d.
Mean 0.20 (8 subjects)		

n.d.=not detected (<0.10 ng/ml)

Table 3. Concentration of Vk_1 in the maternal and cord venous blood (SHEARER). (Vk_1 = vitamin K_1)

Subject no.	Plasma vitamin K_1 (ng/ml)	
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5	n.d.	n.d.
6	0.21	n.d.
7	0.13	n.d.
8	0.26	n.d.
9	0.27	n.d.
Mean 0.20 (8 subjects)		

n.d.=not detected (<0.10 ng/ml)

delivery (table 3).

However, in the present study, when an intravenous infusion of 60 mg of vitamin K_2 was administered to two patients who had elective caesarean section deliveries for cephalo—pelvic disproportion it was found that transfer of vitamin K_2 occurred :

Case 1 : Patient A primigravid and 28 years old. The concentration of plasma vitamin K_2 rose to a peak in one to three hours and declined in seven to eight hours. The pattern is almost similar to that of normal adults and newborn babies, and 5.3 ng/ml VK_2 was detected in the umbilical venous blood (Fig. 5) by liquid chromatography.

Case 2 : Patient B primigravid and 40 years old. Pregnant for 40 weeks. The fetus was in a quiet state, and she was given a slow constant infusion of 60 mg of vitamin K_2 together with 20 ml of glucose one hour before the performance of the caesarean section. A concentration of vitamin K_2 in the plasma of 11,900 ng/ml was found to be highest just after administration. The level of VK_2 was 94 ng/ml in the umbilical venous blood.

The observations from these two case studies are of great importance in view of the fact that, after 60 mg of vitamin K_2 was administered by intravenous infusion six hours prior to c—section a concentration of 5.3 ng/ml of vitamin K_2 was detected in the umbilical venous blood.

When these results are compared with those of Shearer and others, there is a 60 fold difference between the dose of vitamin K_1 (1 mg) and that of vitamin K (60 mg), and 5.3 ng/ml (equivalent to 44 times the previously reported umbilical level of 0.12 ng/ml) of vitamin K_2 was detected.

In the second case, 60 mg of vitamin K_2 together with glucose was administered via a slow intravenous injection. A significantly greater amount of vitamin K_2 (94 ng/ml) was detected in the umbilical blood of this newborn infant compared to that found in the first case. In the second case, the baby was delivered one hour after the administration of vitamin K_2 , and in the first case, the baby was delivered six hours after administration of vitamin K_2 .

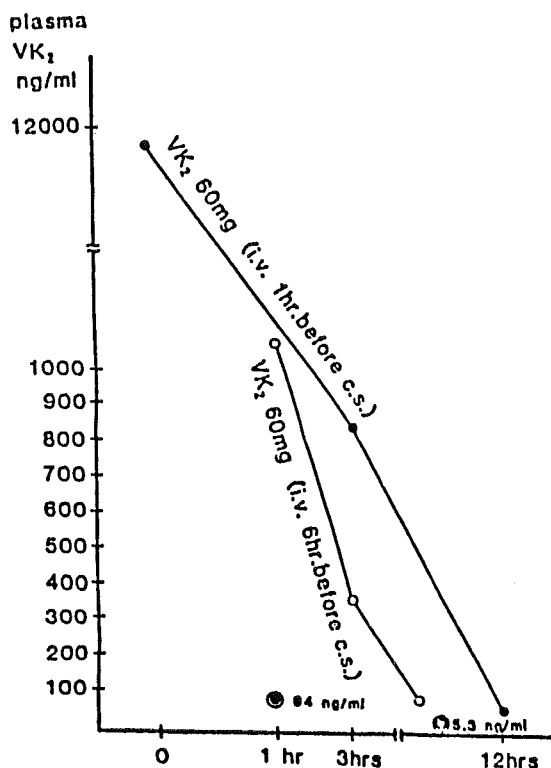


Fig. 5 Concentration of Vk_2 in cord venous blood, after administration to Vk_2 60mg to the mother before Caesarean section.

(Vk_1 = vitamin K_1 , Vk_2 = vitamin K_2)

- concentration of Vk_2 in the mother. (case. I)
- ⊙ concentration of Vk_2 in cord venous blood. (case. I)
- concentration of Vk_2 in the mother. (case. II)
- ⊙ concentration of Vk_2 in cord venous blood. (case. II)

The 94 ng/ml of vitamin K_2 detected only one hour after administration is 17 times the concentration of vitamin K_2 detected in the first case (5.3 ng/ml) after six hours. This suggests that vitamin K_2 crosses the placenta immediately.

It is therefore evident that vitamin K_2 crosses the placenta though not in any great amount. This might be due to a lower level of binding lipoprotein in the fetus which reduces fetal uptake.

We should mention that there are many problems associated with the dosage and timing of administration of vitamin K_2 and estimation of the proportion likely to be transferred to the fetus. It would seem to be necessary to investigate decrease of uptake, as the lipoprotein level becomes lower as pregnancy advances.

4. Can we use prophylaxis against late form of VK deficiency ?

In 1985, the Japanese committee of the Ministry of Health Welfare made the recommendations shown in Table 4.

In Germany the general recommendation was emphasized in 1986 (Table 4). The late form is not seen in countries where routine Vitamin K prophylaxis is performed, as in the USA (Lane and Hathaway, 1985), in Switzerland (Tonz, 1986), and in Sweden (Ekelund, 1986).

The disease is observed in countries without routine Vitamin K prophylaxis such as Japan (Suzuki, 1986), England (McNinch, 1983) and Germany (Sutor, 1986). The data of West Germany from 1983 until the end of 1986 which include many (but certainly not all) patients, suggest a frequency of at least 1 : 50,000 with a tendency to increase.

Table 4. Tentative recommendation of prophylactic administration of vitamin K
JAPAN

All full-term newborns without complication

A dose of 2mg of vitamin K₂syrup (1 ml) is to be given:

within 24h after birth (The syrup is to be diluted with 9ml of water and given after one or two feedings.)

at the age of one week (at the time of discharge)

at the age of one month (at the time of routine checkup) (This dose can be omitted if screening tests are normal.)

West Germany

(1) VK prophylaxis is recommended for all *newborns* with either parenteral (1 mg) administration on the first day of life or repeated oral doses (2 mg) at each of the three routine postnatal examinations, i.e., immediately after delivery, between the third and the tenth day of life, and between the fourth and sixth week of life, preferably in the fourth week. (2) *Premature babies* should receive vitamin K parenterally (0.5–1.0 mg vitamin K). (3) *Babies with disturbed absorption of vitamin K*, i.e., cystic fibrosis, α_1 -antitrypsin deficiency, hepatitis, biliary atresia, or chronic diarrhea, should have vitamin K administered according to prothrombin time (PT) values.

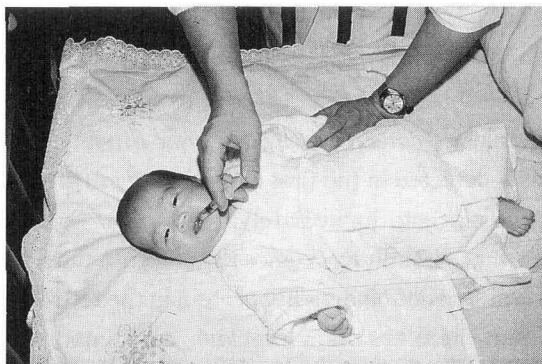


Fig. 7 A dose of 2mg of Vitamin K₂-syrup (1ml) is to be given.

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Another proof of the efficacy of Vitamin K prophylaxis in newborns to prevent the late form of vitamin K deficiency bleeding is the decrease of cases after the recommendation of general prophylaxis in 1986 in West Germany (Fig. 6). The clinical effectiveness of Vitamin K prophylaxis is without doubt, although there was no agreement on the mode of application, the dosage, and the duration among the experts. Most likely the filling of liver stores is responsible for the long term action of Vitamin K prophylaxis.

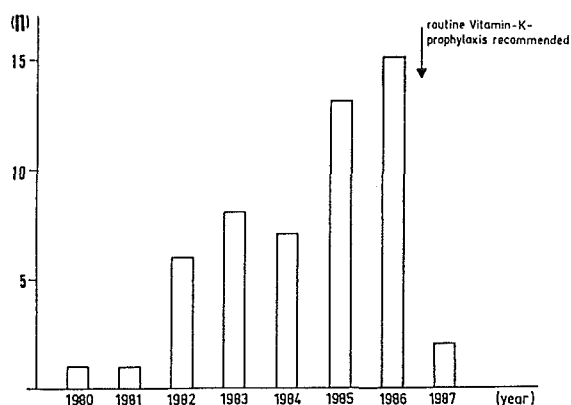


Fig. 6 Late form of Vitamin K deficiency bleeding in West Germany.

Table 5. Hemorrhagic disease due to vitamin K deficiency occurring after the neonatal period, 1978–1985.

	Idio- pathic	Sec- ond- ary	Idiopathic and secondary			Near miss
			Number of cases	Number of births throughout Japan	Number of reported cases per 100000 births	
1978–1980 ^a (Annual incidence)	111	30.3	141.3	1642580 (1979)	8.6	—
1981	98	10	108	1529455	7.1	1
1982	118	11	129	1515392	8.5	10
1983	98	16	114	1508687	7.6	13
1984	82	14	96	1489786	6.4	22
1985 ^b	31	6	37	696869 ^b	5.3	11
Unknown	0	0	0	—	—	2
1981–1985						
Total	427	57	484	6740189	—	59
Annual incidence	94.9	12.7	107.6	1497819	7.2	—

^aData from the first nation-wide survey by Nakayama et al.

^bfrom January to June

Table 5 shows the number of infants suffering from vitamin K deficiency and the rate of vitamin K deficiency per 100,000 births in Japan. These data include both idiopathic and secondary types. The upper line indicates the rate of patients from 1978 to 1979, during which

the first nationwide survey was carried out by Dr. K. Nakayama. Since 1984, the number of reported cases of VKDI has been decreasing slightly.

Although it is not sure if prophylactic administration of vitamin K orally in such doses could prevent the intracranial hemorrhage, it is necessary to establish an active and routine plan in order to prevent this disease, because we know that the incidence of Late Form vitamin K deficiency was very rare in the United States, where vitamin K was routinely given intramuscularly at birth.

We should also think about diet during pregnancy from the view point of vitamin K rich foods, so long as we have proved that vitamin K passed through the placenta, even though it was in small quantities.

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