Vitamin K Deficiency Disease

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Abstract

Vitamin K deficiency bleeding (VKDB) previously known as hemorrhagic disease of the newborn has been classified as Early (0-24hrs), Classic (2-7 days) and Late (1-6 months). Child birth following the maternal ingestion of anti-epileptic drugs such as Phenytoin, is liable to result in early VKDB as well as bone changes in the fetus. Other maternal risk factors for VKDB include medications such as warfarin and antibiotics. Failure to administer vitamin K at birth, prematurity, infective gastro-enteritis, the administration of antibiotics, malabsorption, liver disease, prolonged breast feeding, and malnutrition as shown by hypoabuminemia have all been associated with VKDB. In view of the pivotal role of vitamin K in hemostasis and osteogenesis it is postulated that the bleeding, bruising and fractures seen in some children thought to be non-accidental injuries such as Shaken Baby or Shaken Impact Syndrome, could be due to a deficiency of vitamin K. To investigate this possibility the reports of three affected children were examined. It was found that the coagulation screen showed an increase in the prothrombin time, a normal partial thromboplastin time, a normal or slightly increased level of platelets and an absence of a family history of bleeding – findings consistent with vitamin K deficiency. It is concluded that the lesions hitherto attributed to non-accidental injury are in some cases due to a deficiency of vitamin K alone, and others occur in combination with vitamin C deficiency which is a well documented cause of "battered baby". Vitamin K deficiency is best detected by the Protein Induced by vitamin K absence/abnormality (PIVKA -II) test rather than the prothrombin time and by the serum under-carboxylated osteocalcin test which provides the best guide to the state of mineralization of bone and hence the tendency to fracture. A name change to vitamin K deficiency disease would accommodate both the blood and bone lesions found in this condition when vitamin K alone is shown to be the cause.

Key Words

Vitamin K, Fractures, Non-accidental Injury, Shaken Baby Syndrome, Child Abuse, Vitamin K Deficiency Disease

Introduction

Some unexplained fractures in infants, especially if associated with subdural or retinal bleeding or with external bruising, are currently attributed to child abuse by Child Protection Agencies.

Caffey[1] was the first to implicate parental violence in the etiology of infantile subdural hematomas associated with fractures of the skull and long bones. However, Caffey's initial reports were compatible with, and even suggestive of, infantile scurvy or toxic histaminemia.[2] The first mention of shaking of infants as a cause of subdural hematomas appeared in a paper by Guthkelch[3] before Caffey's paper on the Shaken Baby Syndrome[4] (SBS) was published.

Since then it has become axiomatic in academia that subdural hematomas, associated with retinal hemorrhages, bruising and fractures occurring in infants and young children which cannot be explained by the parents is evidence of non-accidental injury or more specifically the Shaken Baby Syndrome or Shaken/Impact Syndrome.[5-10] It has been suggested,[11] and generally accepted in the English speaking world, that subdural hemorrhages resulting from non-accidental injury can be distinguished from accidental injury by the following:

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1. Age less than 12 weeks
2. Retinal hemorrhages
3. Skeletal fracture
4. Unexplained bruising
5. Inconsistent history

However parents and carers generally vehemently protest their innocence and it is vital, therefore, that the presence or absence of an alternative explanation such as a hemostatic disorder be investigated.[12]

Pregnant women suffering from epilepsy who consume anti-epileptic drugs such as Phenytoin have a significantly greater chance of the child developing vitamin K deficiency bleeding and/or distinctive skeletal abnormalities[13-17] than those not so treated. Other evidence also indicates that vitamin K is intimately associated with defects in hemostasis[18-20] and osteogenesis[21-23] and for these reasons a vitamin K deficiency was sought as an alternative explanation for the alleged Shaken/Impact Syndrome.

Method

Three children with fractures and bleeding who had evidence of vitamin K deficiency are reported. One of these children has been reported previously but the cause of the fracture was stated to have been "undetermined".[24]

Case 1

A male infant was born to a 20-year-old mother after a 41-week gestation by normal vaginal delivery. Vitamin K 1 mg (IM) and hepatitis B vaccinations (Hep B) were given. The child was breast fed for two months and then formula fed. The mother smoked during her pregnancy.

At his routine well check at the age of 2 months, his navel had still not healed, and some bright red discharge was noted. Immunizations consisting of diphtheria, tetanus, and acellular pertussis (DTaP), hemophilus influenzae B (Hib), and Hep B vaccines were given. These were repeated 2 months later.

On the night after the second set of vaccinations, the mother said the infant was irritable. The following day the baby's father gave him a bath and laid him on the bed while he attended to some other matter for about two minutes. When he returned, he found that the infant was limp, unresponsive, and not breathing. Shortly thereafter he became blue and was taken to the emergency department of the local hospital where he was resuscitated and his condition stabilized before other investigations were done.

A skeletal survey showed findings consistent with a non-displaced fracture of the distal left tibia. Blood studies showed:

Prothrombin time 17.9 sec
(normal range, 8.2–14.1)
Partial thromboplastin time 35.5 sec
(normal range, 28.0–50.0)
Aspartate aminotransferase 97 U/L
(normal range, 20–60);
Hemoglobin 11.0 g/dL
(normal range, 10–13.5)
Platelets 382 x 10^9/L
(normal range, 150– 450)

The recorded diagnoses were non-accidental injury and Shaken Baby Syndrome.

Case 2

During her pregnancy the mother was hospitalized once with signs of a kidney and urinary tract infection and treated with antibiotics. She had difficulty in retaining the prenatal vitamins she was prescribed because of morning sickness which lasted the entire nine months of her pregnancy. The child was given an injection of vitamin K at birth and was breast fed.

At the age of 10 weeks blood was noted in his diaper and in his urine.

Urine examination confirmed the presence of blood. No coagulation studies were done at this stage.

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Hematology Report
1. Hemoglobin 11.8g/dL
(normal range, 11.5–16.5)
2. Platelets 506 x 10^9/L
(normal range, 150–500)

Four days later when the father picked up the infant from his crib, he stiffened as though having a seizure and turned red in the face. His lips were purple and he suddenly went limp. The baby stopped breathing and was admitted to hospital.

A skeletal X-Ray showed healing posterior rib fractures of the right 10th and 11th ribs and recent fractures of the anterior aspects of the right 6th and 7th ribs. Extensive subdural blood of mixed density was seen overlying the right greater than left cerebral hemispheres.

Laboratory Investigations.
1.Liver Function Tests
Aspartate aminotransferase 399 U/L
(normal range, 20–60)
Alanine aminotransferase 138 U/L
(normal range, 6–50)
y-Glutamyl transpeptidase 92 U/L
(normal range, 11–82)
Alkaline phosphatase 202 U/L
(normal range, 110–320)

2. Hemorrhagic Screen
Prothrombin time 18.3 secs
(normal range, 11.5–14.5)
International normalized ratio
1.6 (normal range, 0.9–1.2)
Partial thromboplastin time 33.7 secs
(normal range, 24.0–35.0)

A diagnosis of non-accidental injury was made.

Case 3

Shortly before the birth of her child the mother had high fever with vomiting and watery bowel motions. The child was born by vaginal delivery and a large bruise was apparent on the right side of the face involving the eye. The hospital record does not mention the use of forceps. Vitamin K 1 mg was given IM. The infant was formula fed and the mother noticed that the right eye remained closed when the infant was feeding.

Immunizations were carried out at 2 weeks. Following this the mother complained the baby cried literally 20 hours a day and was not feeding properly and had frequent bouts of diarrhea. When 4 weeks old the urine in her diapers developed a strong smell and her gums were noticed to be bleeding.

At the age of 6 weeks the child again had severe diarrhea and was crying. The father tried to console her but he realized something was seriously wrong when the infant stopped breathing, became limp and unresponsive and later became cyanosed. Pinkish fluid was coming from the nose. An attempt at CPR was unsuccessful and the infant was rushed to hospital where she was intubated but failed to regain consciousness and died shortly thereafter.

Laboratory Investigations
Prothrombin time 15.4 secs
(normal range, 11.5–14.0)
International normalized ratio 1.31
Partial thromboplastin time 26 secs
(normal range, 23–34)
Fibrinogen 148 mg/dL
(normal range, 180–490)
Total protein 3.9 g/L
(normal range, 6.0–8.8)
Albumin 2.5 g/L
(normal range, 3.5–5.0)
Platelets 512 x 10^9/L

Urine 4 red cells per high power field.

Radiology
1. CT Scans and X-Rays showed subdural hemorrhage with cerebral edema and healing fractures of the right costovertebral junctions of the 3rd and 4th ribs.

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Postmortem Findings

The autopsy findings confirmed what had already been observed clinically and a diagnosis of Shaken Baby Syndrome was made.

Results

Besides a diagnosis of non-accidental injury or Shaken Baby Syndrome the children reported here have in common:

1. Evidence of intra-cranial bleeding
2. Evidence of fractures
3. Prolongation of the prothrombin time
4. Normal partial thrombplastin time
5. Normal or raised platelet counts
6. "Herald" bleeds – navel, urine, bruise
7. No family history of bleeding or consanguinity.

In no instance was there evidence of disseminated intravascular coagulation (DIC). Thrombocytopenia, microthrombi in the small blood vessels and thrombi in midsize and large arteries and veins which are markers of DIC were not recorded. Although congenital deficiencies of the coagulation factors are known to occur they are rare and most would be detected by prolongation of the partial thromboplastin time and by the family history. It is clear that the finding of a prolonged prothrombin time is thus most probably due to a deficiency of vitamin K. An associated deficiency of vitamin C cannot be excluded particularly in Case 3 in which there was evidence of malabsorption or malnutrition.

Just 50% of the normal concentration of prothrombin is sufficient to produce a normal PT.[25] Prolongation of the PT, even slightly, as in Case 3, is therefore evidence of advanced vitamin K deficiency.

In addition to a prolongation of the prothrombin time Case 2 showed significant abnormalities in the Transaminase levels and is possibly an example of the neonatal hepatitis syndrome in which one expects malabsorption of vitamin K.[26]

Discussion

The blood coagulation proteins Factors II, VII, IX and X and the bone forming proteins osteocalcin and matrix Gla protein, to be functionally active, must be carboxylated by the vitamin K dependent enzyme γ-glutamyl carboxylase. This action converts the glutamic acid residues of these proteins to γ-carboxyglutamic acid which is a calcium binding amino acid required for the function of vitamin K dependent proteins.[23] In the case of the coagulation proteins this function is the formation of a blood clot and the prevention of bleeding while osteocalcin and matrix Gla protein ensure mineralization and strengthening of bone and the prevention of pathological fractures.

The infant's vitamin K comes partly from the mother via the placenta initially and from the breast milk later. It also comes partly from bacterial fermentation in the gut which in the first few days of life is sterile. If the child develops diarrhea, as did the child in case 3, this source of vitamin K is reduced or lost.

Malabsorption of vitamin K in children may be the result of a variety of causes[27] and antibiotic therapy may also lead to vitamin deficiency by destroying the vitamin K forming bacteria in the gut.[28] It is these children that are vulnerable to bleeding and pathological fractures and who should be carefully investigated for an alternative explanation of the findings hitherto attributed to non-accidental injury or to the Shaken Baby Syndrome. Both vitamin K and C are intimately connected with the maintenance of the integrity of bone and hemostasis and both are subject to malabsorption.

The children described here were known to have been given vitamin K at birth as recommended but it is obvious from the prolonged prothrombin time that it was not sufficient to sustain normal health and von Kries[29] has pointed out that the failure rate is about 0.25 per 100,000.

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Osteogenesis is a dynamic process with bone formation and bone resorption occurring simultaneously. Should bone formation be impaired for any reason resorption may predominate with demineralization and fractures the result.

While the role of vitamin K in the prevention of fractures has so far been demonstrated in menopausal women and in subjects with cystic fibrosis in whom there is a malabsorption of fat-soluble vitamin K the evidence of a lack, or abnormality, of vitamin K in the children described here suggests a similar process may be occurring in these children and the fractures are being wrongly attributed to child abuse.

The prothrombin time which is commonly used is not as sensitive as the PIVKA II (Protein Induced by vitamin K Absence/Abnormality) test[25] and the serum under-carboxylated osteocalcin test, while well established in the investigation of osteoporosis and fractures in women, has not been applied to the investigation of unexplained fractures in children

These omissions should urgently be addressed by all laboratories dealing with children.

Conclusion

Vitamin K deficiency or abnormality may have a significant bearing on the etiology of the lesions in children hitherto attributed to non-accidental injury, Shaken Baby Syndrome or physical child abuse. The role of vitamin K is not confined to the prevention of hemorrhagic disease of the newborn/(vitamin K deficiency bleeding) but is also essential for the mineralization and strengthening of the infant's bones. Both the hemorrhagic and osseous lesions of alleged child abuse can be accounted for by vitamin K deficiency. However there appears to exist an association between vitamin K deficiency and vitamin C deficiency as both are subject to malabsorption and malnutrition and it is possible that in some instances of so-called Shaken Baby Syndrome they co-exist.

Proof that there is an association between a prolonged prothrombin time and false accusations of Shaken Baby Syndrome in the cases presented here is provided by the fact that "similar fact evidence is analogous to challenge/de-challenge/re-challenge…" Both are capable of demonstrating causality to the highest standards of proof.[30]

The investigation should start with a careful and thorough history paying particular attention to any medications such as anticonvulsants, anticoagulants or antibiotics given to the mother during her pregnancy which are likely to reduce the vitamin K reaching the foetus. Smoking may reduce the level of vitamin C in the mother's blood and add to the infant's problems.

Some antibiotics given to a child may destroy the vitamin K forming gut bacteria. Diarrhea, vomiting, loss of appetite should arouse suspicion of the possibility of a vitamin K deficiency and appropriate measures taken.

Although all three children showed a significant elevation of the prothrombin time it is the increase in under-carboxylated osteocalcin and PIVKA-II which best reflect the defects in osteogenesis and hemostasis and the investigation should include these tests which are more informative than the prothrombin time. In addition, the common coagulation and liver function tests should also be performed routinely.

Hypoalbuminaemia is one of the first markers of malnutrition and should always be determined.

Finally vitamin K deficiency disease would seem an appropriate diagnosis for children with subdural hemorrhages, retinal hemorrhages, bruises and fractures which the parents cannot explain and the PIVKA-II test is abnormal.

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Conflict of Interest. I have given evidence for the Defence in Courts in England, United States of America and Australia.

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