Vitamin K Deficiency

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Vitamin K refers to a group of fat-soluble compounds. There are several vitamin K-dependent proteins involved in coagulation, bone development, and cardiovascular health. Vitamin K deficiency can contribute to significant bleeding, poor bone development, osteoporosis, and increased cardiovascular disease. According to the National Academy of Science Food and Nutrition Board, the dietary requirements are based on the intake of healthy adults, and the adequate intake is 120 and 90 ug/day for men and women, respectively.

Vitamin K Deficiency Bleeding (VKDB) in newborns can separate into three categories based on the timing of the presentation. Early VKDB presents within 24 hours after birth, classic VKDB presents within the first week, and late VKDB presents between one to twelve weeks of life.

Etiology

Vitamin K deficiency occurs in the neonatal period, in Hereditary Combined Vitamin K-dependent Clotting Factors Deficiency (VKCFD), inadequate uptake from diet or because of a chronic disorder, or it can be drug-related.

Epidemiology

All neonates have reduced Vitamin K at birth. The first reported classic VKDB was in 1894 as a bleeding disorder that occurred on day 2 or 3 of life. In combination with sepsis-induced bleeding, the incidence was 600/100,000 infants with a 62% fatality rate. Late VKDB occurs in 4.4 to 72 infants per 100,000 births with an increased risk in exclusively breastfed infants and the highest incidence occurring in Asian populations. Early VKDB has been associated with mothers on anticonvulsants or other vitamin K interfering substances, and incidence without vitamin K supplementation has been reported as high as 12%. The mortality rate for late VKDB is 20-50%. Late VKDB also has a significant neurologic morbidity rate. Without Vitamin K supplementation, the current day incidence of classic VKDB is estimated to be 0.25-1.7%.

VKCFD is extremely rare with less than 30 cases worldwide and affects males and females equally.

In normal healthy adults, 8-31% have vitamin K deficiency. However, it is very rare to result in clinically significant bleeding. Cases are limited to individuals with malabsorption syndromes and those treated with drugs that interfere with vitamin K metabolism.

Pathophysiology

Vitamin K is a group of fat-soluble 2-methyl-1,4-naphthoquinone. There is a variable alkyl substituent at the third position and exists in two principal forms: K1 (phylloquinone) and K2 (menaquinone). There is a third, synthetic form K3 (menadione), the use of which has been replaced by a synthetic form of vitamin K1 due to the potential for toxicity in infants with

glucose-6-phosphate dehydrogenase deficiency. The primary vitamin K1 is predominantly from leafy green vegetables, while the main source of Vitamin K2 is intestinal flora and fermented foods. Vitamins K1 and K2 have different bodily distributions and may have different impacts on enzyme activity. Vitamin K1 is the major source in the human diet and is absorbed in the jejunum and ileum, transported by chylomicrons in circulation, and is dependent on bile, pancreatic enzymes, and dietary fat content.

These substances are necessary for adequate blood clotting because they are cofactors for gamma-glutamyl carboxylase and vitamin K2,3-epoxide reductase complex in modifying gamma-carboxyglutamic acid on clotting factors II, VII, IX, and X. This modification is required for cofactors to bind to phospholipids in the platelet membrane. Under-carboxylated clotting factors will lead to decreased protein activity and can lead to bleeding.

Vitamin K is also a requirement for various other proteins including anti-coagulant proteins (C, S, and Z), osteocalcin, and matrix GLA protein. Under-carboxylated osteocalcin has shown to increase in individuals with decreased bone mineral density and with increased fracture rates in the elderly. Decreased levels of some vitamin K subtypes result in increased arterial calcification. Vitamin K is not transported across the placenta efficiently, and infants are born with low to undetectable concentrations of Vitamin K and elevation of Protein Induced by Vitamin K Absence or Antagonism (PIVKA). PIVKA is a pre-carboxylated (incompletely carboxylated) form of prothrombin.

VKCFD is an autosomal recessive disorder with mutations in gamma-glutamyl carboxylase (type 1) or vitamin K2,3-epoxide reductase complex (type 2) which results in under-carboxylation and decreased activity of K-dependent proteins.

Complications

Bleeding is the most significant complication because of vitamin K deficiency and is often fatal in infants. Increased fracture rates and cardiac disease may also be a complication. However, more research is required.

History and Physical Examination

Vitamin K deficiency can present with a history of bleeding at venipuncture sites or with minor trauma. The patient may also have a history of antibiotic, anticonvulsant, or other prescription drug use. Additionally, during a physical exam, ecchymosis or petechiae may be found.

In VKDB, the neonate will present with bleeding. Early VKDB often presents with intracranial, intrathoracic, intra-abdominal and other severe bleeding conditions. Early VKDB is also often associated with maternal drugs that inhibit vitamin K metabolism. Classis VKDB typically occurs with less severe bleeding such as that of the umbilicus, gastrointestinal tract, and post-circumcision. Late VKDB often presents with severe intracranial bleed. All forms of VKDB have a high incidence of the refusal of vitamin K prophylaxis. Late VKDB has a higher association with exclusively breastfed infants due to the lower dietary intake of vitamin K found in human milk versus formula. Warning bleeds or bruising should always prompt further investigation by laboratory testing.

VKCFD presents in the newborn period in severe cases similar to VKDB but can present later in life in milder cases. Common presentation occurs with severe spontaneous or surgical bleeding

events. History of easy bruising and mucosal bleeding is frequent, and there can be developmental and skeletal abnormalities.

Diagnosis

Diagnostic criteria for VKDB include a PT greater than or equal to 4 times the normal value and one of the following:

1. Normal or increased platelet count with normal fibrinogen and absent degradation products

2. PT normalization within 30 minutes after IV vitamin K administration

3. Increased levels of PIVKA-II. (PIVKA-II and is a sensitive marker for vitamin K deficiency status)

When VKCFD is suspected as the cause, a research laboratory can be employed to perform genotyping of gamma-glutamyl carboxylase and vitamin K2,3-epoxide reductase complex for confirmation.

Treatment

Prophylaxis in newborns: 1 mg of vitamin K1 by intramuscular injection within 1 hour of birth. Alternatively, 2 mg of vitamin K1 orally at birth, at 4-6 days and at 4-6 weeks. Another alternative oral administration is 2 mg Vitamin K1 at birth and a subsequent weekly dose of 1 mg for three months. Intramuscular injection is preferable for efficacy.

VKDB: 1 to 2 mg vitamin K1 by slow intravenous or subcutaneous infusion. Severe bleeding may require fresh frozen plasma at a dose of 10-15 mL/kg.

Vitamin K deficiency due to malabsorption: Dependent on the disease. Malabsorption requires daily administration of high doses of oral vitamin K1 0.3 to 15 mg/day. If oral dosing is ineffective, consideration should be for parenteral vitamin K1.

VKCFD: 10 mg vitamin K1 2-3 times per week by an oral dose by intravenous infusion. Fresh frozen plasma may be required during surgery or in cases of severe bleeding at a dose of 15-20 mL/kg. Prothrombin Complex Concentrates and recombinant Factor VII may also have utility during surgery or severe bleeding.

Vitamin K nutritional deficiency in adults: At least 120 and 90 ug/day for men and women respectively, by diet or oral supplementation to meet the National Academy of Science Food and Nutrition Board recommended intake.

Chronic conditions: As more research becomes available, a larger dosage of oral vitamin K1 and K2 may be beneficial. No present guidelines are available.

Toxicity and side effect management

There are no known adverse effects of excessive intake of dietary vitamin K. Phytonadione is a synthetic derivative of vitamin K1 and is available as an oral tablet or inject able emulsion that is available for administration by intravenous, intramuscular or subcutaneous routes. Reports of anaphylactic reactions are rare but are an estimated incidence of 3/10,000 doses, and associations point to the intravenous route in more severe cases. The emulsifying agents, specifically

polyoxyethylated castor oil, have been implicated as the cause of the anaphylactic reaction in most cases.

References

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