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Mariam Ayyash

Meera Chitlur

Johannes Oldenburg

Majid Shaman

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Suspected vitamin K-dependent coagulation factor deficiency in pregnancy: A case report

Mariam Ayyash [a,*], Meera Chitlur [b], Johannes Oldenburg [c], Majid Shaman [d]

[a] Department of Obstetrics and Gynecology, Henry Ford Hospital, Detroit, MI, United States of America
[b] Department of Hematology Oncology, Detroit Medical Center Harper University Hospital, Detroit, MI, United States of America
[c] Institute of Experimental Hematology and Transfusion Medicine Bonn, University Clinic Bonn, Bonn, Germany
[d] Division of Maternal and Fetal Medicine, Department of Obstetrics and Gynecology, Henry Ford Hospital, Detroit, MI, United States of America

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ABSTRACT

Hereditary combined vitamin K-dependent clotting factor deficiency (VKCFD) is a rare autosomal recessive congenital bleeding disorder. There are no established guidelines for the care for pregnant women and newborns within the context of VKCFD. A 39-year-old multigravida woman with a family history of VKCFD was referred for high-risk maternal fetal medicine care. Prenatal testing for fetal VKCFD was declined. The patient received vitamin K1 from 36 weeks of gestation and had an uncomplicated vaginal delivery. The baby had normal head ultrasound results, vital signs, and physical examination, with no signs of bleeding: factor levels and coagulation factors were within reference range. Follow-up showed no evidence of VKCFD. A thorough care plan is required for pregnant women whose newborns are at risk for VKCFD.

1. Introduction

Vitamin K is required for the conversion of glutamic acid residues to gamma carboxyglutamic acid within prothrombin precursors for the synthesis of procoagulant factors II, VII, IX, and X and anticoagulant factors Protein C and Protein S, which are necessary for calcium-dependent binding and normal blood coagulation [1–3]. Hereditary combined vitamin K-dependent clotting factor deficiency (VKCFD) is a rare autosomal recessive congenital bleeding disorder characterized by decreased levels of the vitamin K-dependent pro- and anticoagulant factors; and vitamin K-dependent proteins involved in calcium homeostasis, bone and cartilage formation [4–6]. VKCFD can manifest as a spectrum of presentations, with severity ranging from mild to severe [7]. The first case of VKCFD was described in 1966, in a female newborn who exhibited significant bleeding from the first week of life [8]. The child was born from an uncomplicated pregnancy and had symptoms manifesting as bruising beginning at week 1 of life, with recurrent serosanguinous oozing from the umbilical stump throughout the first months of life. The diagnosis of VKCFD is extremely rare. Currently, fewer than 30 VKCFD kindreds have been reported worldwide [9–11]. Very little data exist on VKCFD within the context of pregnancy. This report highlights the case of a pregnant woman with a family history of VKCFD and outlines a comprehensive care plan for perinatal care when VKCFD is suspected.

2. Case Presentation

A 39-year-old multigravida Yemeni American woman was referred to the high-risk maternal fetal medicine service because of a family history of VKCFD. The patient was in a consanguineous marriage. She and her husband were half first cousins; their fathers were half-brothers. She had 2 male children and 1 female child. This was the couple's fifth pregnancy together, and the patient had had one first-trimester miscarriage. Their 14-year-old son was diagnosed with VKCFD when he was between 18 and 24 months of age, when he was seen in the emergency room for extensive facial bruising after he walked into a door. The bruising was deemed to be more than expected and an extensive diagnostic workup during the hospitalization identified VKCFD. Their 6-year-old son was subsequently diagnosed with VKCFD at birth and had significant developmental delays and a speech impairment. Both sons had skeletal and dental manifestations. Both patient's sons were under the care of hematology and were being treated with vitamin K. Their 11-year-old daughter was also tested at birth and was unaffected and healthy.

An amniocentesis was offered to the patient, with a special consideration that required knowing her affected sons' genetic variants. The patient declined an amniocentesis for possible prenatal diagnosis of

* Corresponding author at: 2799 W Grand Blvd, Detroit, MI 48202, United States of America.
E-mail address: mayyash1@hfhs.org (M. Ayyash).

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VKCFD and declined cell-free fetal DNA blood testing and carrier screening. The patient was confirmed to be a carrier of a heterozygous missense mutation, which both affected children were noted to be homozygous for. Of note, the patient herself had no prior bleeding problems within and outside of pregnancies. Her deliveries were all uncomplicated.

Given that VKCFD is an autosomal recessive disease, there was a 25% chance of the fetus being affected. The patient was started on 10 mg of vitamin K1 supplementation daily at 36 weeks of gestation to facilitate an increase in vitamin K-dependent factor levels and potentially prevent severe intrauterine bleeding complications such as intracranial hemorrhage.

Because of the risk involved in having a child with VKCFD, the patient was closely followed during the monthly perinatology conferences and a concrete plan was made in collaboration with the maternal fetal medicine department and the pediatric hematology department (Table 1). The plan included the following: in the antepartum period, (1) daily maternal supplementation with 10 mg of vitamin K1 starting at 36 weeks; in the intrapartum period, (2) avoid fetal scalp electrode and (3) avoid instrumentation during delivery unless urgently indicated; in the immediate postnatal period, (4) obtain cord blood after delivery to determine diagnosis, (5) draw factor levels II, VII, IX, and X at birth to determine whether the child is affected with the condition, (6) permit intramuscular vitamin K supplement and hepatitis B vaccine to the newborn while applying pressure for 10 min and applying ice if bruising is significant, (7) perform a thorough physical examination on the newborn to ensure no bruising or petechiae and monitoring for bleeding after the newborn screening heel stick, and (8) obtain a head ultrasound of the newborn after birth to confirm no intracranial hemorrhage; in the early postnatal period, (9) hold off on performing circumcision until factor levels are within a healthy range if the child is male; and lastly in the late postnatal period (10) if the newborn is stable, discharge with the mother and perform any necessary follow-up testing at a specialized pediatric hospital.

The patient had an uncomplicated antenatal course. She presented in labor after spontaneous rupture of membranes at 40 weeks of gestation. She had an uncomplicated vaginal delivery of a female neonate, with Apgar scores 8 and 9 at 1 and 5 min of life, respectively, with a quantitative blood loss of 72 mL. The baby had normal head ultrasound results, normal vital signs, a satisfactory physical examination, and showed no signs of bleeding. Factor levels and coagulation factors were drawn after delivery. Overall, the baby had normal coagulation factor levels (Table 2). The baby had normal newborn follow-ups at 2 weeks and 2 months of life and subsequently.

Table 1
Care Plan for pregnant women with VKCFD or whose newborns are at risk of VKCFD.

Period	Plan
Antepartum	- Daily maternal supplementation with 10 mg of vitamin K1 starting at 36 weeks
Intrapartum	- Avoid instrumentation at delivery unless necessary - Avoid fetal scalp electrode
Immediate postnatal	- Obtain cord blood - Draw factor levels II, VII, IX, and X as well as prothrombin time and partial thromboplastin time - Performing a thorough newborn physical examination - Permitting intramuscular vitamin K supplement and hepatitis B vaccine to the newborn while applying pressure for 10 min and applying ice if bruising was significant - Obtain newborn head ultrasound
Early postnatal	- Hold off on performing circumcision until factor levels are reported
Late postnatal	- Discharging neonate with the mother and performing any necessary follow-up testing at a specialized pediatric hospital

Table 2
Coagulation factor levels for the newborn.

Coagulation Labs	Level	Reference range
Internal normalized ratio	1.23	Unknown
Prothrombin time	15 s	10–15.3 s*
Partial thromboplastin time	37 s	31.3–54.5 s*
Factor II	50%	26%–70%
Factor VII	74%	50%–150%
Factor IX	26%	50%–150%
Factor X	41%	50%–150%

* M.Andrews, B Paes, M Johnston. Development of the haemostatic system in the neonate and young infant. Am J of Ped Hem/Onc. 12(1): 95–104, 1990.

3. Discussion

Hereditary VKCFD is an extremely rare condition. The two genes associated with the VKCFD are *GGCX* (gamma-glutamyl carboxylase) and *VKORC1* (vitamin K epoxide reductase complex subunit 1) [12,13]. Making the appropriate diagnosis can allow for differentiating the genetic form of the disorder from the acquired forms, which can be caused by intestinal malabsorption of vitamin K, liver or renal dysfunction, or poor dietary intake. The first sequence variant in the *GGCX* gene was identified in four members of an Arab family who had combined deficiency of all vitamin K-dependent procoagulants and anticoagulants [14]. The affected individuals had skin ecchymosis starting soon after birth, and central nervous system bleeding that was diagnosed at the age of 6 weeks. Laboratory results for those individuals showed prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT). They also showed no response to 1 mg vitamin K; however, weekly treatment with 10 mg vitamin K was successful in preventing bleeding episodes after several years of follow-up, and hence, vitamin K administration at birth might delay the diagnosis of VKCFD in neonates [15].

Symptoms of VKCFD can vary and correlate with coagulation factor levels [16]. Affected newborns can be symptomatic at birth with spontaneous intracranial hemorrhage or umbilical stump bleeding [11,14,17]. Alternatively, they can be asymptomatic at first and present later in childhood with spontaneous hemarthrosis or soft-tissue or gastrointestinal bleeds [15]. Older individuals can have easy bruising or post-surgical bleeding [18,19]. Other manifestations in more severely affected children with the *GGCX* mutations, include skeletal abnormalities such as bone hypoplasia, conductive hearing loss, and mental retardation [20–22].

Most patients with VKCFD show partial or complete improvement in factor activity, as well as normalization of PT and aPTT with oral or parenteral vitamin K [18,20,23]. These patients have an excellent prognosis. In some cases, though, vitamin K is ineffective and there is biochemical evidence that the molecules are not fully carboxylated by vitamin K treatment [3,24]. The response to vitamin K varies based on the route of administration and the individual's sensitivity to vitamin K [25]. A fixed therapeutic regimen has not been identified, and no clear correlation exists between clinical severity and responsiveness to vitamin K [7]. Continued daily treatment with high-dose oral vitamin K has been successful in preventing some bleeding complications and is recommended for patients with VKCFD [3,23]. One case report also suggested possible value in administering fresh frozen plasma for VKCFD in pregnancy while another suggested the use of prothrombin complex concentrates, which contain factors II, VII, IX, and X, and proteins C and S [23,26].

In patients who are heterozygous for the mutation, such as this case, while the mother had a negative history of bleeding during or outside of pregnancy, it is also important to initiate vitamin K supplementation to also potentially prevent intrauterine or perinatal bleeding complications. The dose and timing of initiation of this therapy (at onset of pregnancy vs. third trimester) is still under investigation. In those with the *GGCX* mutation, there may be some benefit to starting early to

potentially prevent the bone and skin manifestations.

From a neonate standpoint, before performing genotyping for *VKORC1* and *GGCX*, it is important to rule out other differential diagnoses for vitamin K deficiency such as liver disease, malabsorption, or ingestion of warfarin, anticonvulsants, or antibiotics [27]. Checking prothrombin time and activated partial thromboplastin time after birth can be helpful screening tools post-delivery in suspected cases, but specific factor activity measurements are essential to establish the appropriate diagnosis in the child [27]. In addition to those factors, additional systematic steps should be kept in mind to ensure proper care, including a thorough examination, head ultrasound, holding off on circumcision, and ensuring proper follow-up testing at a specialized pediatric hospital.

In summary, this report emphasizes the importance of having a proper plan in place for when a suspected coagulopathic disorder such as VKCFD is present, in order to prevent and manage potential bleeding in the peripartum period. Early detection and management lead to a good prognosis overall. This report adds to the limited literature on VKCFD in pregnancy and outlines a plan of care for pregnant women with VKCFD or whose newborns are at risk of VKCFD.

Contributors

Mariam Ayyash cared for the patient, conceived the idea for the case report, wrote the manuscript, obtained consent from the patient and revised the manuscript.

Meera Chitlur provided hematology expertise care for the patient throughout her pregnancy and reviewed and edited the manuscript.

Johannes Oldenburg provided hematology expertise and reviewed and edited the manuscript.

Majid Shaman provided maternal-fetal medicine expertise care for the patient throughout her pregnancy and reviewed and edited the manuscript.

All authors approved submission of the manuscript.

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Patient consent

Consent was obtained from the patient.

Provenance and peer review

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Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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