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Case report

Coagulation factor XIII deficiency – Report of a newborn *F13A1* Val34Leu polymorphism carrier

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Abstract

Coagulation factor XIII deficiency (FXIIID) is a rare inherited autosomal recessive bleeding disorder. FXIIID is the only coagulation factor deficiency that has been associated with pregnancy loss. Regarding neonates, prolonged umbilical cord bleeding and intracranial hemorrhage, a life-threatening condition in the neonatal period, have been reported in cases with inherited FXIIID. In this report, we present a case of a newborn of a homozygous *F13A1* Val34Leu variant mother, while reviewing the current literature.

Keywords

F13A1 Val34Leu, polymorphism, recurrent pregnancy loss, prolonged umbilical cord bleeding, intracranial hemorrhage.

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Introduction

Coagulation factor XIII (FXIII) deficiency (FXIIID) is a rare inherited autosomal recessive bleeding disorder with an incidence of 1:1,000,000-2,000,000, but 10-fold higher in countries where consanguineous marriages are observed [1, 2]. Its classification depends on the defect being either in the *F13A1* or in the *F13B* gene [3]. The *F13A1* deficiency (type I), also called quantitative deficiency, is the most common. The *F13B* deficiency (type II), also called qualitative deficiency, accounts for < 5% of cases [4]. Combined type I and II deficiencies are even rarer [5]. Both types of FXIIID result in the absence of the catalytic action of the activated FXIII (FXIIIa) [6].

Concerning the clinical phenotype, FXIIID can lead to recurrent miscarriage, severe bleeding and impaired wound healing [4, 7, 8]. In this report, we present a case of a newborn of a homozygous *F13A1* Val34Leu variant mother.

Case presentation

A 37-week gestational age female neonate was born, in a private maternity clinic, through cesarean section from a 29-year-old mother, due to intrauterine growth restriction (IUGR). The Apgar score was 8 and 8 in the 1st and 5th minute, respectively. Her birth weight was 2,170 g. She developed respiratory distress gradually, received O_2 with headbox and was transferred at the 7th hour of life to our Neonatal Intensive Care Unit (NICU) for further management.

At admission, her Downes score was 3, with mild retractions and respiratory rate > 80. She received intravenous (IV) ampicillin and gentamycin, due to possible perinatal infection, and started IV dextrose with 4 mg/kg/min. The rest of the laboratory examinations were normal for her age. She was a symmetric small for gestational age (SGA) neonate with 31 cm head circumference and 46 cm body length.

The child's mother had FXIIID and was homozygous for the *F13A1* Val34Leu polymorphism. Her family history is reported free. The diagnosis was made with PCR-STRIP assay analysis (**Fig. 1**). Moreover, she was heterozygous for the methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C mutations, as well as for the beta-fibrinogen G-554->A mutation. She was under *per os* acetylsalicylic acid and IV enoxaparin. Her pregnancy was uncomplicated. On the 36th week of gestation, the fetus presented IUGR and the mother received steroids due to an imminent cesarean section.

During the hospitalization, the newborn received O_2 with headbox for 48 hours. On the 2nd day of life started minimal feeding along with the parenteral feeding, and on the 3rd day of life, we ruled out the possible perinatal infection (negative blood culture and CRP) and the antibiotic therapy was stopped. The respiratory distress was attributed to transient tachypnea. She did not present any bleeding diathesis, like delayed umbilical cord bleeding or intracranial hemorrhage. Finally, on the 8th day of life, she was discharged.

Discussion

FXIII, also known as fibrin stabilization factor, is a protransglutaminase, a plasma tetramer proenzyme that consists of 2 A and 2 B subunits of 83.2 kd and 79.7 kd, respectively [9]. The A subunit's gene coding (*F13A1*) is localized on chromosome 6p25.1, providing protein's catalytic properties, while the B subunit's gene coding (*F13B*) is localized on chromosome 1q31.3. Subunit B is the plasma protein acting as the carrier of the A subunit [10, 11]. During activation of FXIII and in the presence of Ca^{2+}, the B subunits dissociate from the tetramer resulting in two active FXIII-A monomers [12]. The FXIIIa acts as transglutaminase catalyzing the formation of gamma-glutamyl-epsilon-lysine by crosslinking the α and γ chains of fibrin, while it crosslinks as well with the α2 plasmin inhibitor chains. As a result, FXIIIa plays an important role in the stabilization of the fibrin clot and its lysis [13, 14]. Apart from its role in the coagulation mechanisms, FXIIIa contributes to angiogenesis, wound healing, vascular permeability as well as in cardio-protection and the maintenance of pregnancy [15].

In our case presentation, the mother had no history of recurrent miscarriages. What is more, the mother, as well as the neonate, had no bleeding diathesis.

The first case described in the literature with FXIIID presented impaired wound healing [8]. Nevertheless, approximately only 30% of FXIIID cases present with this phenotype [16-18].

FXIIID is the only coagulation factor deficiency that has been associated with pregnancy loss [19]. The maternal FXIII-A subunits accumulate at the placenta, in the area where the fetal and maternal tissues join, developing a cytotrophoblastic shell.

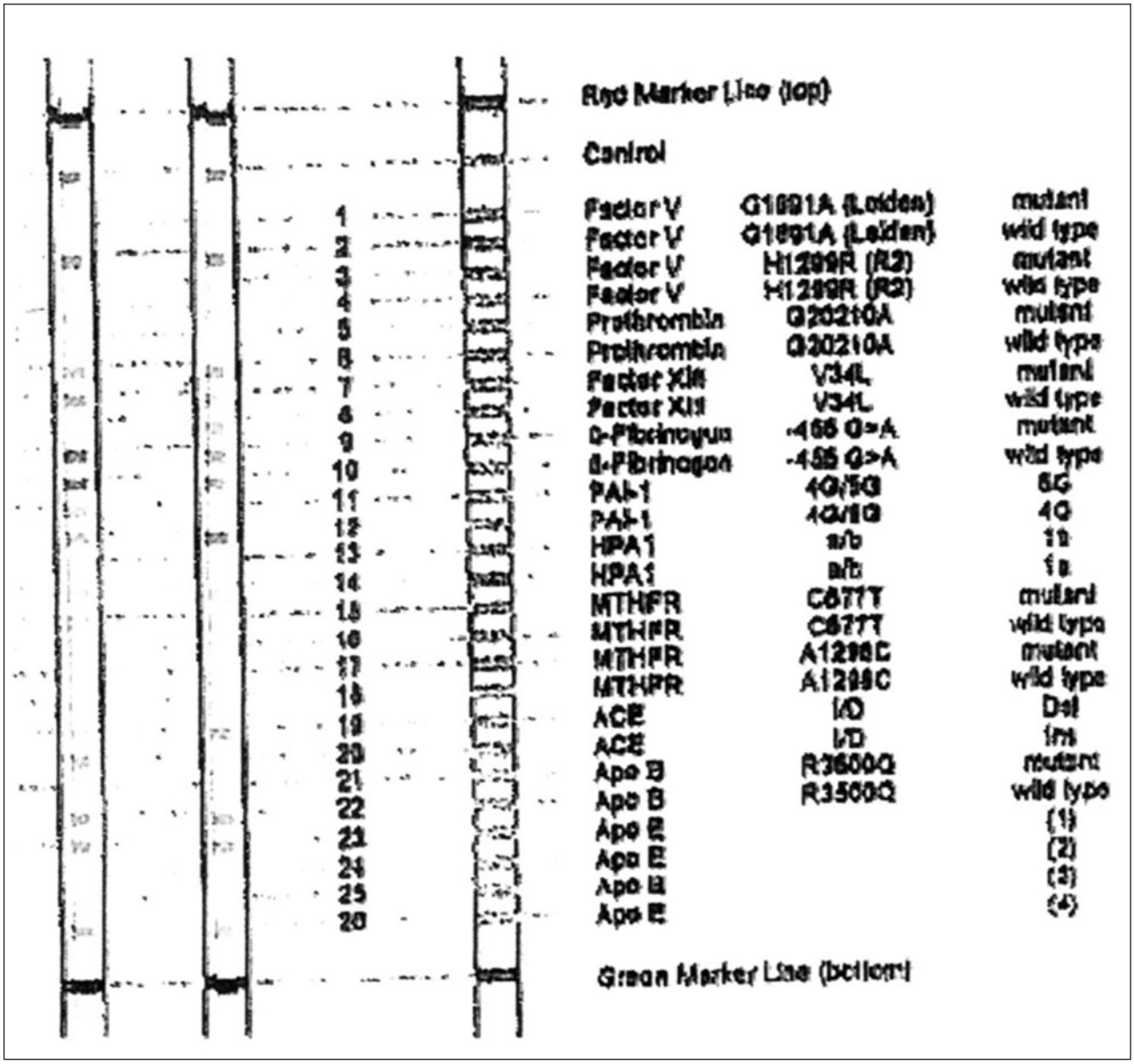

Figure 1. PCR-STRIP assay of the mother.

In FXIIID, this cytotrophoblastic shell probably does not develop, leading to placental abruption and consequent miscarriage [20].

Regarding neonates, prolonged umbilical cord bleeding has been reported to 73-83% and intracranial hemorrhage, a life-threatening condition in the neonatal period, to 17-30% of cases with inherited FXIIID [16-18]. Thus, it is imperative that, in the presence of prolonged cord bleeding, the neonatologist should be alert to request laboratory tests for FXIIID.

Five frequent polymorphisms have been described in the *F13A1* gene; Val34Leu, Tyr204Phe, Pro564Leu, Val650Ile and Glu651Gln [9]. Glu651Gln and Val650Ile have not been associated with any disease [9]. Pro564Leu polymorphism has been associated with an increased risk for stroke (OR 4.3, 95% CI 1.4 to 13.7), especially in women with intracerebral hemorrhage and in smokers [21].

Tyr204Phe polymorphism is the rarest of these polymorphisms with a frequency of 0.01-0.03 per million in the general white population. It has been associated with an increased risk for recurrent miscarriages, even though only 0.5-2% of normal FXIII levels are sufficient to achieve normal hemostasis and this polymorphism leads to almost normal FXIII activity. It has been suggested that FXIII may crosslink with other substrates than fibrin, and that the increased risk for miscarriages may be associated with the structure of FXIII and not its level or activity [22].

Val34Leu is the most common polymorphism, with a frequency of 0.25-0.30 per million in the general white population, and has a protective role to thrombotic disease [13, 14]. The FXIII levels in plasma are not affected, but the activation of FXIII proceeds 2-3 times more rapidly [23, 24]. This acceleration leads to a change in the structure of the crosslinked fibrin [25]. The changes in fibrin structure result in a reduced fibrin clot with reduced mass/length ratio fibers [26]. Studies have shown an association of Val34Leu polymorphism with decreased risk of myocardial infarction, coronary artery disease and a weak protective effect in venous thromboembolic events [14, 27, 28].

While in the current literature there has been no association between Val34Leu polymorphism and the pregnancy outcome, or events in the neonate, a meta-analysis of Jung et al. in 2017 revealed that the *F13A1* Val34Leu polymorphism was associated with recurrent pregnancy loss in the Asian population [29]. It is known that racial factors along with gene-to-gene and gene-to-environment interactions can affect the FXIII activity [30, 31]. Moreover, recurrent pregnancy loss is multifactorial. Therefore, studies regarding only one gene, as well as a single population, without taking into consideration the aforementioned interactions, could produce results that are confounded.

Regarding the observed case, recurrent miscarriages and bleeding disorders are equally absent. Given the FXIIID studies that have been published, this clinical phenotype is confirmatory of the current literature. However, genetic recombination potentials and genes' interaction are an active process, so gene polymorphisms and variants in correlation with clinical phenotype should always be recorded and considered in everyday clinical settings' improvement.

Abbreviations

FXIII: factor XIII
FXIIIa: activated FXIII
FXIIID: FXIII deficiency
IUGR: intrauterine growth restriction
MTHFR: methylenetetrahydrofolate reductase
NICU: Neonatal Intensive Care Unit
SGA: small for gestational age

Declaration of interest

The Authors declare that there is no conflict of interest. Funding: none.

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