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Factor VII Constitutional Deficiency: Singularity of a Family Case

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Abstract

Factor VII or proconvertin is a vitamin K-dependent plasma glycoprotein synthesized by the liver. Factor VII deficiency is suspected with the combination of an elongated Quick time and a normal activated partial thromboplastin time. Constitutional deficits are very rare and have autosomal recessive transmission; they are also phenotypic ally and genotypic ally very heterogeneous. This case is about a child of first-degree relatives, who was admitted to pediatric emergencies for important epistaxis requiring transfusion. The biological assessment showed a normal partial thromboplastin time (TCK) with a low prothrombin level, suggesting a problem in the exogenous pathway of coagulation. The Factor VII assay showed a deficit evaluated at 2%. Screening was conducted among parents and siblings and revealed the presence of the deficit in all family members in various degrees, which adds to the singularity of this case.

Keywords: Constitutional; Deficit; Factor VII; Family; Epistaxis.

Introduction:

Factor VII or proconvertin is a plasma glycoprotein synthesized by the liver in the presence of vitamin K. Factor VII deficiency or Alexander's disease is a very rare condition, manifesting itself in a hemorrhagic syndrome of variable expression ranging from simple epistaxis to deadly cerebral haemorrhage [1,2,3]. The originality of this observation lies in the revelation of a congenital factor VII deficiency in a small child of 6 years after a first bleeding episode of major epistaxis that required resuscitation measures; and the screening of the rest of the family members that revealed the existence of deficiency among all the family members as well.

Observation:

J.M, female child, 6 years old, the youngest child of consanguineous relatives in the first degree, with a 13-year-old sister, occasionally having gingival bleeding of low abundance, never explored; and a 9-year-old brother who had never had a bleeding syndrome before. J.M was admitted to pediatric emergencies at Mohammed VI University Hospital in Marrakech for important epistaxis, with hemodynamic disorders, occurring spontaneously without the notion of trauma. This condition motivated her hospitalization in pediatric resuscitation. The clinical examination at her admission found a conscious child, with marked mucocutaneous pallor, active epistaxis of great abundance, a blood pressure of 90/60 mm of mercury and a running pulse. The rest of the somatic examination was normal.Resuscitation measures were initiated (two good-sized peripheral venous routes, saline-filling protocol) and balloon probe tamponade was performed. The initial biological assessment revealed a normocytic normochromic anemia at 6,6 g.dl-1, a prothrombin time (PT) at 18% (N = 70% - 100%) and normal values for activated thromboplastin time (control = 32s) and fibrinogen (N = 2-4 g / l).The blood grouping was A

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rhesus +, and the direct Coombs test was negative. In view of this clinical picture, suggesting a deficit in the exogenous coagulation pathway, a functional factor VII assay was performed, and the result showed an estimated deficit of 2% (normal: 70-140%). Antigenic research could not be performed.The patient received a transfusion of red blood cells and fresh frozen plasma (FFP) that stabilized and improved her hemodynamic state. Screening at parents showed a factor VII deficiency in the mother at 48% and in the father at 59%. The 9 years old brother, asymptomatic, revealed a factor VII deficiency with a rate of 2%, and the older sister, reporting a hemorrhagic diathesis type gingival bleeding, presented a rate of 5%.

Discussion:

Congenital or hereditary factor VII deficiency is very rare. Its incidence is estimated at 1 / 500,000 to 1 / 1,000,000 [1]. On the other hand, one in 500 can carry the defective gene located on chromosome 13 [1,4]. Factor VII deficiency is one of the very rare causes of haemorrhagic syndromes in children [1,3]. It is a hereditary disease of autosomal recessive inheritance, hence its frequency in consanguineous marriages [1], which is the case in our observation, where one of the particular points is the transmission of the defective gene in the three children of the couple.

There are indeed two types of factor VII deficiency: constitutional deficiency transmitted by parents and acquired deficit secondary to other conditions (hepatopathies, malignancies, certain drugs ...) [1,5,6].

Factor VII deficiency results in a hemorrhagic syndrome which remains the main symptom and is observed in homozygous subjects, a heterozygous subject is very rarely affected [1,5,7]. Some studies report that a rate below 30% is more likely linked to a homozygous deficit, while rates above this value are linked to a heterozygous deficit. This would suggest that in the observation that we report, the three children of this heterozygous couple would carry the defective gene in a homozygous way, which adds to the singularity of this family case.

The severity of bleeding is variable and according to several studies, does not seem related to the importance of the deficit [1,2]. However, some authors report that the lower the factor VII, the more serious the bleeding [1,2]. So more than 20% of normal: the bleeding is discreet; from 5 to 20% of normal: bleeding is moderate and from 1 to 5% of normal: bleeding is important [1,2].Our patient falls into this category, and presented an episode of major epistaxis; his brother is also in this category but has always been asymptomatic, while the older sister, aslo in this category, occasionally had low abundance gingivorrhagia, which confirms the independence of the bleeding severity towards the depth of the deficit. This classification is not a general rule, because according to studies, some patients with FVII levels below 15% may be completely asymptomatic even during surgeries, while some patients with higher values may have hemorrhagic episodes but exceptionally severe [8].

According to the literature, the most frequent bleeding are those after tooth extraction, epistaxis and hemarthrosis [3]. From the symptomatic point of view, there are four clinical forms of the disease [1,2]: a severe form at birth and infancy: characterized by haemorrhage at cord drop and intracranial haemorrhage, it is necessary to note that neonates are at high risk of intracranial

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hemorrhage, in fact, one out of six newborns with this deficiency will have intracranial bleeding [1]; a serious form with onset in the early childhood (our patient's case): most often it is a haemorrhage during the fall of the baby teeth or at puberty which results is abundant menorrhagia, but also epistaxis; a mild form with a late onset sometimes in adulthood with pathological bleeding after trauma or after surgery; and an almost asymptomatic form discovered during a genetic survey or preoperative assessment.

The positive diagnosis is based on biological elements: an elongated Quick time evoking an abnormality of the exogenous pathway and a normal TCK assuring integrity of the endogenous pathway [5,7].Confirmation is provided by the factor VII functional assay, usually by a chronometric technique, it is the measurement of the time of Quick of a mixture with equal volume of the plasma of the patient diluted to 1 / 10th and of the reagent plasma deficient in factor VII, the measured time is converted into percentage of activity by referring to a calibration curve established from a control plasma having 100% activity[5,7].

When a hereditary deficiency is suspected, the second step of the biological diagnosis is based on the factor VII antigenic research [5,7,9]. In specialized laboratory, the antigen assay can be carried out by immunological method to differentiate a quantitative and a qualitative deficiency, Elisa techniques have replaced immunoelectrophoretic or radioimmunoassay techniques [9]. As well, the search for the mutation responsible for a constitutional deficit can be done by molecular biology but not falling under of current practice [5,7].

The treatment of constitutional factor VII deficit is substitutive, but the indications remain difficult to pose in the absence of consensus, particularly on the haemostatic rate of factor VII [1,6].The treatment is based on symptomatic measures indicated during acute bleeding, and consists of : the administration of 10 to 15 ml / kg of fresh frozen plasma, which may be effective, but which has certain drawbacks, in fact the FFP contains relatively a little amount of factor VII, and many need to be administered to provide the required amount of factor VII, not to mention the risk of viral transmission[1,6]; the administration of PPSB concentrate is being used less and less because of the high risk of thromboembolic complications [1,6]; and administration of factor VII concentrate, knowing that 0.5 U / kg increases the proconvertin level by 1% [1,6] (not available in our context).Long-term prophylaxis for severe and repetitive bleeding may be required at the rate oftwo injections per week of factor VII concentrate [1,2]. Perioperative prophylaxis may be indicated too: 20 U / kg before the intervention with the intention of achieving a rate of 40%; and postoperatively: 5 to 10 U / kg per eight hours for 5 to 10 days to maintain a 20% rate [1,2].

Regarding genetic counseling and given the extreme phenotypic heterogeneity of FVII deficiency, including asymptomatic individuals, genetic counseling will depend on the clinical impact of the condition in a given family. Only the existence of a first child with very severe manifestations can lead to an antenatal diagnosis during a subsequent pregnancy [10].

Conclusion:

Congenital factor VII deficiency, although exceptional, poses real therapeutic and prognosis problems given the lack of correlation between the severity of the bleeding and the biological data, illustrated by this family case, especially that genotype-phenotype relationships are not

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currently clearly defined, and the lack of consensus on the hemostatic factor VII ratio, which makes the therapeutics choices difficult.

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