

THE FACTOR VII DEFICIENCY IN MOROCCAN CHILDREN

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Abstract:-

The Factor VII deficiency is a rare causes of bleeding disorders in children. 12 cases were diagnosed and treated in hematology and oncology service between 2003 and 2016. The clinical manifestations are extremely variable. The severity of bleeding is variable and does not seem related to the importance of the deficit; a deep deficit may remain asymptomatic or result in more or less severe hemorrhagic syndrom. 33% of cases were asymptomatic, 66% of cases had a hemorrhagic syndrom: its Mucocutaneous bleeding (33%), gastrointestinal bleeding (17%), Urinary bleeding (hematuria) (8%), Articular bleeding (haemarthrosis ankle) (8%). Our patients have low PT ranging from 12% to 55%. Family investigation is required, including the dosage of Factor VII in parents and siblings. The Factor VII deficiency is suspected ahead of the combination of an elongated prothrombin time and a normal PTT, it is confirmed by the dosage of factor VII activity, by chronometric method. Replacement therapy of this deficit is not systematic, it is indicated in the case of an acute hemorrhagic stroke, or prophylactically prior to surgery, it is based on the recombinant Factor.

Keywords: - factor VII, deficiency, children, bleeding disorders.

INTRODUCTION:-

The Factor VII deficiency is a rare bleeding disorder first described in 1951 by Alexander. The hereditary deficiency is an autosomal recessive disorder, characterized by a clinical, biological and molecular variability. The diagnosis is made by the determination of Factor VII level. The treatment is indicated in the case of an acute hemorrhagic stroke, or prophylactically prior to surgery. It is factor replacement therapy. Our aim through this study is to study the factor VII deficiency in Moroccan children, make an epidemiological approach, describe the clinical and para-clinical of the disease, discuss the clinicobiological correlation, and make an update on the treatment.

MATERIALS AND METHODS:

It is a retrospective descriptive and analytical study, conducted over a period of 13 years from 2003 to 2016, in the Hematology and Oncology service of Rabat in the Children's Hospital of Rabat. We included in our study all children under the age of 15, who were diagnosed and treated in our department after the consent of both parents.

A scorecard has been established to analyze the study records, together epidemiological data, and the circumstances of discovery, clinical and biological aspects and therapeutic data. Our service is located at the children's hospital of Rabat, in the university hospital of the capital of Morocco. It is the largest service in Morocco in terms of area, capacity and infrastructure. It supports children with cancers (acute leukemias and malignant solid tumors), thalassemia, sickle cell disease, haemophilia, haemorrhagic diseases, immune deficiencies and other diseases of the blood. It serves the regions of Tangier-Tétouan-Al Hoceima and Rabat-Salé-Kénitra. Data exploitation and statistical analyses were performed with SPSS.

RESULTS:

We collected and analyzed 12 cases (Table 1) diagnosed at Hematology and Oncology service of Rabat: 8 Boys (66% of cases) and 4 girls (33% of cases). The median age of our patients was 5 years (minimum age: three months, maximum age: 13 years). The sex ratio was 2. 66% of cases were boys. Fifty-eight percent of our patients came from a low socio-economic level. Half of our patients come from a consanguineous marriage. His notion of hemorrhagic diseases in the family was found in one case; the sister presented a hemorrhagic syndrome with recurrent epistaxis, her factor VII rate was 3%. A family survey was conducted in ten patients, including making family tree, determination of prothrombin time (PT), partial thromboplastin time (PTT) and factor VII in parents and siblings. The family nature of factor VII deficiency was found in 4 patients, while it was sporadic cases in other patients.

As for the mode of revelation:

- ❖ 4 patients (33% of cases) were asymptomatic at diagnosis. A hemostasis test including a PT and a PTT were asked preoperatively, objectifying a low PT and normal PTT. The dosage of factor VII was low.
- ❖ 8 patients (66% of cases) had a hemorrhagic syndrome:
 - Bleeding mucocutaneous:
 - Epistaxis (Two patients).
 - Post dental extraction haemorrhage. (One Patient)
 - Gastrointestinal Bleeding:
 - Hematemesis. (One patient)
 - Rectal bleeding. (One patient)
 - Post circumcision hemorrhage (one patient).
 - Urinary haemorrhage (Hematuria) (one patient).
 - Articular bleeding (haemarthrosis ankle) (one patient).

Biologically, our patients have a low PT level ranging from 12% to 55%. PTT level is normal in all patients.

The level of factor VII is low ranging from 2.1% to 47.2%.

The level of factor VII:

- Less than 5% in 3 patients (17% of cases).
- Between 5 and 20% in one patient (17% of cases).
- More than 20% in 8 patients (66% of cases).

A dosage of PT and PTT was conducted among parents and siblings of 10 patients:

- The PT is normal in 8 fathers, pathological in 2 fathers (34% and 60%).
- The PT is normal in 8 mothers, pathological in 2 mothers (25% and 50%).
- The PT of both parents was pathological in one patient mother PT = 25%, father TP = 34%.
- The PT was measured among the siblings of our patients, it is pathological in one sibling of 3 patients, and in two siblings of one patient.

A dosage of factor VII level was conducted among parents and siblings of 10 patients:

- Factor VII level are low in 3 parents (a father with normal PT) **ranging** from 34% to 42%.
- Factor VII levels are low in 3 mothers (mothers had a normal PT) ranging from 25% to 55%.
- Factor VII levels are low in one sibling of 3 patients, and in two siblings of a patient, ranging from 3% to 25%.
- The level of factor VII of the parents was pathological in two patients.

One family member of a patient (a sister) was symptomatic (epistaxis).

Therapeutically:

- ❖ 7 patients (58% of cases) were transfused with fresh frozen plasma (FFP).
- ❖ 2 patients (17% of cases) required a transfusion of red blood cells associated with the FFP.
- ❖ One patient received the factor VII (eptacog alfa activated NOVOSEVEN *)
- ❖ 3 patients (25% of cases) did not require treatment.

Evolution

- ❖ A patient with a factor VII level of 21%, in whom the diagnosis of factor VII deficiency was carried out during a preoperative inguinal hernia and who received FFP transfusion preoperatively, presented in postoperative a scrotal hematoma. The patient showed a good evolution under FFP.
- ❖ A patient, in whom the diagnosis of factor VII deficiency was carried out after a hemarthrosis ankle at the age of five (level of factor VII at 4%), presented at the age of thirteen a menorrhagia related to a pelvic hematoma. The patient required transfusion of packed red blood cell, FFP and hormonal treatment.

DISCUSSION:

FVII is a clotting factor vitamin K-dependent. It is a glycoprotein of 406 amino acids secreted by the liver and whose half-life is between 4 and 6 hours. Its mean plasma concentration corresponding to a coagulant activity of 100% is 0.5 mg / ml (10nM). A small proportion of fVII circulates in the enzymatically active form (fVIIa), but it was only in the presence of its receptor, the tissue factor, that fVII ,after auto activation to fVIIa, develops its full activity on its physiological substrates , FIX and FX. This step is considered to be the initiation of the physiological cascade of coagulation. The involvement of multiple actors in the action of fVII may explain why there is no direct relationship between plasma and hemorrhagic expression, unlike the deficit in factor VIII or IX for example. [1]

The analysis of the literature suggests a neighboring threshold value of 10% below what the surgical bleeding risk becomes significant [2, 3] but the risk assessment is usefully supplemented by the identification of the causal mutation. The FVII gene contains 9 exons for a total length of 12,8kb [4]. It is located on the chromosome13 (13q34) near the fX gene. More than 130 mutations responsible of constitutional deficiency fVII were reported. A majority of them affect exon 9 (catalytic domain, 1,6kb). The distribution of mutations depends on the geographical origin [5] and at least two polymorphisms of the F7 gene are involved in the phenotypic heterogeneity deficits.

Conversely, patients with the R304Q mutation in the homozygous or double heterozygous state associated with another mutation are usually asymptomatic or pauci-symptomatic, despite sometimes fVII rate <1% .The R304Q mutation is found in <1% of symptomatic cases on a large series of 717 cases of deficits FVII [7].

The Factor VII deficiency is one of the rare causes of bleeding disorders in the children. Its incidence is, probably underestimated because many deficits do not have clinical expression, it is estimated at 1/500 to 1/1 000 000 000. In contrast, one in 500 can be a carrier of the defective gene. [6, 7] 12 cases were diagnosed and monitored in hematology and oncology service between 2003 and 2015.

The Factor VII deficiency is an autosomal recessive disorder which means that both parents must carry the defective gene in order to pass it on, it reaches both girls and boys and is most prevalent where consanguineous marriages are frequent. In our series 2/3 of patients are male. And half of the patients are from consanguineous marriage. The family survey conducted with 10 of our patients, found the heritability character of the factor

VII deficiency within 4 patients:

- 1st family: asymptomatic factor VII deficiency in the father (FVII = 42%) and brother (FVII = 28%)
- 2nd family: asymptomatic factor VII deficiency in the father (FVII = 33.9%), the mother (FVII = 55%) and the sister (FVII = 49%).
- 3rd family: asymptomatic factor VII deficiency in the mother (FVII = 50%) and the two brothers (FVII = 25% and 23%).
- 4th Family: asymptomatic factor VII deficiency in the father (FVII = 34%), the mother (FVII = 25%) and symptomatic factor VII deficiency (epistaxis) in the sister (FVII = 3%).

It is sporadic cases for the 5 other patients. The clinical manifestations are extremely variable. A deep deficit may remain asymptomatic or result in more or less severe hemorrhagic syndrome (mucocutaneous hemorrhage (epistaxis, menorrhagia). From The symptomatic point of view, there are four clinical forms of the disease [8]:

➤ **A severe form at birth and infancy:**

Characterized by bleeding at the fall of the cord and by intracranial haemorrhage. Newborns are exposed to a significant risk of intracranial haemorrhage. According to some studies, a newborn out of six affected with this deficit will present intracranial bleeding. Few observations of brain hemorrhages related to Factor VII deficiency have been reported. We collected in our study two infants, aged 3 months and 20 months, having submitted respectively a post circumcision bleeding and a gastrointestinal bleeding (hematemesis type). No case of cerebral hemorrhage was found in our study.

The revelation mode of FVII deficiency in our series of under 4 years olds is gastrointestinal bleeding (2 cases), post circumcision haemorrhage (1 case) and preoperative assesment (3 cases).

- **A severe form with onset in the childhood:** dental bleeding (one case in our series) or menorrhagia at puberty, (one case in our series).
- **a mild form with a late start as adults :** pathological bleeding after a trauma or after a surgical intervention;
- **An almost asymptomatic** discovered during a genetic investigation or preoperative assesment (33% of our patients).

In a study of Herrmann, comprising 717 patients, the clinical symptomatology includes various forms [5]. Are observed, in decreasing order of frequency: epistaxis (58% of cases), menorrhagia (57%), easy bruising (37%), mucosal bleeding (25%), hematoma (20%), hemarthrosis (12%), hemorrhage gastrointestinal (12%), hematuria (7%) and intracranial hemorrhage (1%). extraction haemorrhage (8% of the cases), Haemorrhage post circumcision (8% of the cases).

- gastrointestinal bleeding (17% of the cases):
- Hematemesis 8% of the cases. Rectal bleeding 8%of the cases.
- Urinary bleeding (hematuria) in 8%of the cases.
- Articular bleeding (haemarthrosis ankle) in 8%of the cases.

The Factor VII deficiency is suspected ahead of the combination of:

- An elongated prothrombin time evoking an abnormality of the exogenous path
- A normal PTT ensuring integrity of the endogenous path.

In fact, all our patients have low PT ranging from 12% to 55%. PTT levels are normal in all patients. The dosage of factor VII activity by chronometric method using a plasma deficient in factor VII then identifies isolated deficiency. ormal values are between 70% and 140%, defined relative to a normal plasma pool. In our study, the levels of factor VII is down, ranging from 2.1% to 47.2%. For some variant, the dosage can depend on the reagent (thromboplastin) used. The use of human recombinant thromboplastin could allow a better standardization [9].

Family investigation is required, including the dosage of Factor VII in parents and siblings. [10] The correlation between the severity of bleeding and the importance of the deficit is not proven, and the symptoms are variable, A Profound deficit may remain asymptomatic or result in more or less severe hemorrhagic syndrome. [3, 11, 12].

- 4 of our patients are asymptomatic, their factor VII levels are respectively: 21.5%, 25%, 34% and 39%.
- A patient, with factor VII level at 25%, presented a urinary bleeding.
- 3 of our patients with factor VII levels at 41%, 47.2% and 41% (a factor VII levels higher than asymptomatic patients) had respectively, a nosebleed, a post circumcision bleeding and a gastrointestinal haemorrhage.

Thus, there is no correlation between the severity of the hemorrhagic syndrome and the residual activity of factor VII, if the rate of the factor VII remains superiour to 20%. Three severity levels, however, were distinguished according to the depth of the deficit:

- Rate of factor VII below 5% (17% of cases in our study).
- Between 5% and 20% (17% of cases in our study).
- Superior to 20% (66% of cases in our study).

Some authors report that the lower the facteur VII levels are, the more serious the bleeding is [8]

In fact, two patients in our series, with factor VII rate of 2.1% and 4%, had severe symptoms:

- Important post dental extraction bleeding, recurrent with each tooth loss, requiring FFP transfusions and the use of alpha Eptacog NOVOSEVEN *
- Hemarthrosis ankle and menorrhagia at puberty requiring transfusion of FFP, red cell and hormone therapy.

The treatment by using the concentrates of coagulation factors enables to temporarily increase the level of factor VII in the blood, sufficiently to stop or prevent bleeding. The treatment is indicated in the case of an acute hemorrhagic stroke, or prophylactically prior to surgery. The factor VII deficiency increases the risk of bleeding during surgery, although its importance is not always correlated with the plasma concentration. In fact, surgical procedures were performed in 13 patients with levels of factor VII between 0.1 and 22%, without replacement therapy, although at the time, the administration of PPSB was possible in deficient patients factor VII [13]. In this series, only two patients had hemorrhagic syndrom, successfully treated with blood transfusion. Two of our patients, asymptomatic, with a factor VII rate of 34% and 39%, who had tonsillectomy without receiving replacement therapy, showed no peri or postoperative haemorrhage.

The FFP administration is inefficient because of its low content of Factor VII, leading to transfusion of excessive volumes. It has long been advocated, with 10 to 15 ml/kg, although the half-life of Factor VII is short (3-6 hours). Therefore, some doctors recommend to administrate it by continuous transfusion [14]. 58% of cases in our series were transfused with FFP in default of rFVIIa. Two asymptomatic patients with factor VII levels at 21.5% and 25%, received FFP preoperatively. The postoperative course was uneventful for one, while the other (surgery to cure a hernia) presented a scrotal hematoma with good evolution under FFP. The plasma activated factor VII has been used for the first time successfully in a hemophiliac carrier of an inhibitor, in 1983. Since 1996, a Factor VII of recombinant origin (rFVIIa) has been placed on the market. It is characterized by excellent efficiency and excellent tolerance. It is indicated in the treatment of patients

with hemophilia, factor VII deficiency, and in Glanzmann's thrombasthenia. [15] The dose depends on the indication. The substitution of deficit fVII is currently based on the administration of rFVIIa (NovoSeven®)[16]. During deficits in factor VII, the recommended dose is 15 to 30 mg / kg every 4 to 6 hours, until the bleeding is controlled. One of our patients received rFVIIa (NovoSeven®), she has a factor VII rate at 2.1% and presented extensive bleeding after tooth extraction, she received the NovoSeven in 3 other preventive dental extractions without bleeding complications. When surgery is planned, prophylactic injections are indicated: 20 to 30 mg / kg of Factor VII are administered preoperatively and 5 to 10 mg / kg every 4 to 6 hours after surgery for 5 to 10 days [16, 17]. In case of serious and repeated bleeding, long-term treatment with 2 injections per week was suggested by some authors [18]. The rFVIIa significantly reduces the consumption of blood products and avoids the extension of the duration of hospitalization, caused by excessive bleeding, but it has a high cost. Arterial thrombotic risk [19] as well as the venous risk [20] of rFVIIa, when used at a dose of 90 mg / kg outside its original indication in hemophilia with inhibitors, have been established. A therapeutic amenorrhea may be indicated at puberty, when the deficit recognized in childhood is severe. This is the case of one of our patients: diagnosed with factor VII deficiency at the age of 5, with factor VII levels at 4%. At puberty, the patient presented menorrhagia associated with pelvic hematoma, requiring transfusion of FFP and PRBCs. She was put under hormone therapy. Finally, interdisciplinary collaboration is imperative between: obstetrician, pediatrician, geneticist and biologist for better management.

CONCLUSION

The Factor VII deficiency is a rare inherited disorder. The severity of bleeding is variable and does not seem related to the importance of the deficit; a deep deficit may remain asymptomatic or result in more or less severe hemorrhagic syndrome. Some authors point out, however, that the lower the rate of Factor VII is, the more severe the bleeding is. The Factor VII deficiency is suspected ahead of the combination of an elongated prothrombin time and a normal PTT, it is confirmed by the dosage of factor VII activity, by chromometric method. The prognosis of this disease, accessible to therapeutic, remains linked to the risk of occurrence of serious bleeding, including brain, during neonatal period. Replacement therapy of this deficit is not systematic, it is indicated in the case of an acute hemorrhagic stroke, or prophylactically prior to surgery, based on the recombinant Factor.

AGE	SEX	CONSA- GUNI- TY	REVELATIO- N MODE	PT %	PT T	FACT- OR VII	TREATM- ENT	COMPLICATIO- NS
3 Years et 8 months	M	2 nd degree	Asymptomatic (Preoperative: Inguinal hernia)	46 %	1	21.5%	FFP in preoperative	Scrotal hematoma (FFP)
3 months	M	-	Bleeding post circumcision	50 %	1	47.2%	FFP	
3 year s and a half	M	-	Asymptomatic (Preoperative: Adenoidectomy)	44 %		25%	FFP in Preoperative	
7 year s and a half	F	1 st degree	Asymptomatic (Preoperative: Tonsillectomy)	53 %	1.5	39%		
4 year s	M	-	Asymptomatic (Preoperative: Tonsillectomy)	50 %	1.2	34%		
6 year s	F	1 st degree	Post tooth extraction bleeding	14 %	1.1	2.1%	Tranexamic acid. NOVOSE- VEN.	Two other dental extractions under Novoseven: no bleeding..
1 year and 8 months	F	2 nd degree	Hematemesis	24 %	1	5%	FFP	
13 year s	M	1 st degree	Hematuria	41 %	1	25%		
5 year s	F	2 nd degree	Hemarthrosis ankle	12 %	1	4%	FFP + PRBCs	Hemorrhage / pelvic hematoma: FFP + hormonal TTT.
6 year s	M	-		55 %		41%	Local Hemostatic	
3 year s	M	-	Rectal Bleeding	47 %	1	41%	FFP	Intermittent epistaxis
6 year s	M	-	Sd anemic Rehearsals epistaxis	14 %	1	7.3%	FFP + PRBCs + ttt martial	

Table 1: Characteristics of our patients.

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