Hereditary Factor VII deficiency in 17 Iraqi patients

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Summary:

Background: *The objective of this study is to (1) determine the most common presenting and frequent hemorrhagic symptoms, in Iraqi patients suffering from F.VII deficiency, (2) The figure of prothrombin time ratio that make the physician suspect hereditary F. VII deficiency.*
Patients and Methods: *This is a retrospective study conducted by reviewing the records of 760 patients registered in the center of congenital coagulation disorder in Al.mansour teaching hospital.*
All patients who diagnosed as factor VII deficiency were included in this study. The diagnosis was based on prolonged PT with normal PTT and bleeding time. Clinical information regarding age, presenting features and blood group were also considered.
Results*: out of 760 patient registered in the center of congenital coagulation disorders, 17 patients were considered as having F.VII deficiency; they constitutes 2.2% of all recorded patients.*
The most common presenting feature was haemarthrosis (37.5 %) followed by intracranial bleeding (18.7%) and ecchymosis (18.7 %) .
The most common haemorrhagic symptom recorded was haemarthrosis (50%), epistaxis (50%) followed by ecchymosis (43.7%) .
Patients with in intracranial bleeding constitute 25%. The majority of patients (88.2%) have prothrombin time ratio of more than 3.5
Conclusion : *Hereditary F.VII deficiency should be suspected in :*
1- Children presented with haemarthrosis, intracranial bleeding, epistaxis or ecchymosis
2- Children show prothrombin time ratio of 1.3 and more with normal PTT and normal bleeding time.
Keyword: *Hereditary F.VII deficiency , Prothrombin time ratio.*

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Introduction

Haemostasis is initiated by exposure of tissue factor (TF), which form an active complex with factor VII (TF. VIIa) [1] .

The TF/FVIIa complex leads to the formation of an initial small amount of thrombin through the activation of factor X[2] .

Thrombin activates factor VIII, V, XI and platelets. Negatively charged phospholipids exposed on the surface of platelets activated by thrombin provides an ideal template for the formation of larger amounts of thrombin needed to generate a stable fibrin clot [1]

Factor VII is a vitamin K dependent glycoprotein[3], and levels of 3-10 U/dl are frequently adequate to prevent serious bleeding, but the presence of only trace levels has been associated with major haemorrhages [4].

The synthesis of the factor is controlled by Factor VII gene which is located on long arm of chromosome 13 adjacent to the factor X gene [5]. Factor VII gene is affected by 2 types of mutation:
Type 1 mutation correspond to when both the activity and antigen levels are proportionally reduced, while type 2 mutation correspond to when the antigen level of F VII is normal, but the activity is reduced e.g. dysfunctional [3]. Hereditary F VII deficiency is a rare autosomal recessive disorder, when sever(<1%) cause bleeding similar to that seen in Haemophilia A or B [3] with serious bleeding tendencies [4]. The incidence of the disorder is-1- in 500 000 and both sexes are affected [6,7].

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A long prothrombin time (PT) with normal partial thromboplastine time (PTT), normal thrombin time (TT) and normal platelet count indicate factor VII deficiency, but factor assay is confirmatory [3,5,8].
A normal Russell's viper venom time (RVVT), in which the snake venom directly activates factor X, with prolonged prothrombine time may be useful for the diagnosis of factor VII deficiency [4].
Replacement therapy is necessary to control the haemorrhagic risk. Transfusion of fresh frozen plasma has been used, as well as prothrombin complex concentrate and plasma-derived F VII concentrate. Recombinant activated F VII (or r-F.VIIa) developed in late eighties, can be used in dose of 20 - 30 ug/kg body weight and it is clinically effective[9].

Patients and Methods:

This is a retrospective study conducted by reviewing the records of all patients registered in the center of congenital coagulation disorder in Al.mansour teaching hospital, in the period between July 1997 and September 2003.
All patients who were diagnosed as factor VII deficiency based on prolonged PT with normal PTT and bleeding time were included in this study. Clinical information regarding age, presenting features and blood group were also considered.
The PT was carried out using thromboplastine which is called Esimat –ISI=1.90(bioMerieux) while the PTT was performed using Cephalite (bioMerieux) and bleeding time was performed using Duke method.

Results :

Out of the 760 patients registered in the center of congenital coagulation disorder, 17 (10 males + 7 females) were diagnosed as having factor VII deficiency, they constitutes 2.2% of all patients ; their age were ranged from 1 day to 16 years , and they belong to 15 families .

Table I shows the demographic features , haemorrhagic symptoms and prothrombine time ratio of these patients .

Table II : the demographic features , haemorrhagic symptoms and prothrombine time ratio of the patients .

Family	Patient	Age at Presentation	Sex	Bl. group	Presenting feature	PT ratio	Haemarthrosis	Epistaxis	Ecchymosis	I.C. Bleeding	Post surgical	gum bleeding	Menorrhagia
1	I	11y.	M	A +	Haemarthrosis	53/13 = 4.0	+	+	+				
2	I	13 y.	M	O +	Haemarthrosis	61/12 = 5.0	+			+			
3	I	1 day	M	AB +	Epistaxis	64/12 = 5.3		+	+			+	
4	I	16 y	F	O +	Menorrhagia	75/15 = 5.0		+				+	+
5	I	1 y	F	B +	Post-surgical bleeding	52/12 = 4.3	+	+	+		+		
	II	2.5 y	M	B +	Gum bleeding	63/15 = 4.2					+	+	
6	I	7 y	M	O +	Ecchymosis	17/13 = 1.3			+				
7	I	48 day	F	O +	I.C.bleeding	80/13 = 6.1				+			
8	I	3 y	F	A +	Ecchymosis	50/13 = 3.8			+				
9	I	16 y	M	O +	Haemarthrosis	55/12 = 4.5	+	+				+	
10	I	7 m	F	B +	I.C.bleeding	72/12 = 6.0			+	+			
11	I	-	F	O +	Haemarthrosis and epistaxis.	42/12 = 3.5	+	+					
12	I	6 m	F	O -	Haemarthrosis with ecchyosis	54/12 = 4.5	+	+	+				+
	II	1 d	M	O -	Epistaxis	56/12 = 4.6	+	+					
13	I	13 y	M	O +	Haemarthrosis	65/12 = 5.4	+						
14	I	1.7 y	M	O +	I.C. bleeding	75/13 = 5.7				+			
15	I	8 y	M	O +	n.r.	26/13 = 2.0							

y : year d : day m : month. n.r. : not recorded

The most common presenting feature was haemarthrosis (37.5%) , followed by intracranial bleeding (18.7%), and ecchymosis (18.7%) .
The most common haemorrhagic symptom recorded was haemarthrosis (50% = 8/16) also epistaxis (50% = 8/16), followed by ecchymosis (43.7% = 7/16) , while 37.5 % (6/16) of patients showed both symptoms (haemarthrosis and epistaxis)
Patients with intracranial bleeding constitutes 25% (4/16).Table II

Table II : the prevalence of haemrrhagic symptoms in patients with F.VII deficiency .

Symptom	No. of patients	Prevalence
Haemarthrosis	8/16	50 %
Epistaxis	8/16	50 %
Ecchymosis	7/16	43.7%
I.C. bleeding	4/16	25 %

Thirteen percent of families have more than one patient suffering from F.VII deficiency. Fifty nine percent of patients are males , and Sixty five percent of patients are of blood group O. The prothrombin time ratio showed wide range , from 1.3 to 6.1 The majority of patients (88.2%) have prothrombin time ratio of more than 3.5, (70.5%) have prothrombin time ratio of 3.5 - 5.5, while 17.6% have prothrombin time ratio of more than 5.5, and these patients suffered from intracranial bleeding. (Table III)

Table III : The distribution of prothrombine time ratio among patients of F. VII deficiency .

PT ratio range	No. of patients	Percentage
Less than 3.5	2.0	11.8 %
3.5 - 5.5	12.0	70.6 %
More than 5.5	3	17.6 %

Discussion

The classical entity of hereditary coagulation factor deficiency is Haemophilia A, in which excessive bleeding into various parts of the body, soft tissue haematomas and haemarthrosis are highly characteristic of the disease[10]. Intracranial haemorrhage is not common, but often fatal [10] [11].
In this study, the most frequent haemorrhagic symptoms recorded in patients with factor VII deficiency were haemarthrosis , epistaxis and ecchymosis, but our patients differ from patients of haemophilia A by the more frequent epistaxis; our result are similar to that obtained by Mariani and Mazznucconi, who recorded that haemarthrosis and epistaxis are the most frequent symptoms in patients with F.VII deficiency, followed by haematoma (Table IV) [12].
Table IV: bleeding manifestations in patients with factor VII deficiency.

n.r.= not recorded.

Symptom	Prevalence in Iraqi patients (%)	Prevalence in the study of Mariani (%)
Haemarthrosis	50	66
Epistaxis	50	62
Haematoma	-	45
Ecchymosis	43.7	-
CNS bleeding	25	n.r.

Peyvandi, et al, had also reported the high frequency of epistaxis in their patients. These observations, indicate the importance of the study of platelet function in F.VII deficient patients , as epistaxis is more typical of platelet disorders , than coagulation defect[12]. Rangi et al pointed out a relatively high prevalence of CNS bleeding (16 %) which is simillar to that obtained by peyvandi et al (17 %)[12] ; in our study CNS bleeding showed slightly higher prevalence (25%) . The presence of more than one patient in 13 % of families, reflects the hereditary nature of the disease, and as the disease has autosomal pattern, it is expected to affect males and females equally, in this study, the disease was more frequently encountered in males than females; this may be due to the more activity of males, which make males more subjected to traumatic bleeding.
The prothrombin time ratio showed wide range (1.3 -6.1) reflecting the wide range of the activity of F.VII in the patients, but as the majority of patients (88%) have prothrombin time ratio of more than 3.5, this indicates that most of the studied patients have sever form of F.VII deficiency and this results was consistent with the results of peyvandi et al, who showed that most of their patients have F.VII activity of less than 1 %[12]; therefore, it is prudence to suspect F. VII deficiency in any patient presented with haemorrhagic symptom with a prothrombin time ratio of 3.5 and more and normal PTT and bleeding time.

On the whole, this study demonstrate that:

1- Haemarrthrosis , Intracranial haemorrhage , Ecchymosis are the most presenting features in Iraqi patients suffering from F.VII deficiency .
2- Epistaxis is one of the most common symptom in these patients.
3- Prothrombin time ratio of more than 1.3 with normal PTT and bleeding time lead to the suspicion of F. VII deficiency.

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