Factor XI deficiency: Importance of von Willebrand factor level on haemorrhagic phenotype.

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OBJECTIVE

In patients with factor XI deficiency, bleeding manifestations are weakly correlated with plasmatic factor XI level.
Previous studies suggested that von Willebrand (VWF) activity may influence bleeding tendency in these patients (1).
The goal of the present study is to analyze the clinical and biological characteristics of FXI deficient patients in relationship with haemorrhagic diathesis.
This retrospective observational study was conducted in the "Multisite Grand Est Haemophilia Competence Center" (including the academic hospitals of Besançon, Dijon, Nancy and Reims).

PATIENTS AND METHODS

Population : 177 patients followed in the "Multisite Grand Est Haemophilia Competence Center" .
Inclusion criterion : FXI deficiency patient < 40 IU/dL (using an aPTT-based test with factor XI deficient plasma) .
Exclusion criterion : associated haemostasis deficiency other than vWF deficiency.

Haemostasis screening included platelet count, VWF:Ag, VWF:RCo.
ABO blood group was recorded.

Patients were classified in four groups according to bleeding severity :
- no bleeding
- minor (rare episodes of epistaxis, gum bleeding, easy bruising, menorrhagia...)
- moderate (haematoma, frequent and prolonged bleeding whatever the site)
- major bleeding requiring factor XI replacement therapy or blood transfusion.

Statistical analysis was performed using ANOVA. Statistical significance was defined by p value < 0.05.

Table 1. Age at diagnosis, FXI and VWF level according to bleeding severity

	No bleeding N=68	Minor bleeding N=52	Moderate bleeding N=40	Major bleeding N=17	Level of significance
Median age at diagnosis (range)	14 (0-74)	21 (3-77)	22 (3-63)	34 (13-79)	P<0.001
FXI level (mean ±SD)	26±10	27±10	23±11	22±13	NS
VWF activity (mean±SD)	89±32	87±34	72±33	69±27	P=0.01
VWF antigen (mean±SD)	97±35	91±24	82±36	77±27	P=0.009

Table 2. Clinical situations : surgery, pregnancy and invasive procedure

	Patient number	Event number	Bleeding complications
Surgery : - Multiple dental extraction - Tonsillectomy - Hysterectomy - Appendicectomy - Caesarean section - Orthopedic surgery	N=144	N=345 N=51 N=46 N=11 N=31 N=27 N=42	58 (17%)
Delivery Replacement therapy	N=66	N=135 N=12	20 (15%)
Invasive procedure	N=64	N=93	25 (27%)

RESULTS

Patients (n = 177) were analyzed. Main characteristics were : sex ratio (M/F=0.57), median age (27 years, 3-82), median age at diagnosis (19 years, 0-79), circumstance of diagnosis (incidental=63%, family history=25%, bleeding=12%), blood group O (55%), number of patients with FXI < 15 IU/dL (n=25), positive family history of bleeding (48%).
The repartition of age at diagnosis, FXI level, VWF activity and antigen according to bleeding severity are presented in Table 1.
Main bleeding symptoms were : easy bruising (46%), menorrhagia (30%), gingivorrhagia (27%), and epistaxis (21%).
Bleeding severity is not statistically correlated with FXI level (p=0.08). On the contrary, VWF activity and antigen are correlated with haemorrhagic manifestations (p=0.01 ; p=0.009).
Surgery (n=345), invasive procedure (n=93), pregnancy (n=135) are summarized in table 2. Fertility index is normal in our population (2.04 child / woman). Surgeries were frequent and did not exhibit excessive bleeding complications despite no systematic prophylactic replacement therapy (91%). In 37% of cases, bleeding complications did not require any specific intervention.

CONCLUSIONS

As expected, bleeding tendency is mild in our patients and bleeding severity is not statistically correlated with FXI level.
On the contrary, VWF antigen and VWF activity are correlated with haemorrhagic manifestations (respectively p=0.009 and p=0.01).
VWF significantly influences bleeding tendency in FXI deficient patients. VWF:Ag measurement can be performed easily in most laboratories. Thus, we suggest to measure VWF in all patients with FXI deficiency in order to predict more accurately the haemorrhagic risk and to adapt the care of the patient for surgical, invasive procedure or obstetrical situation.

REFERENCES:

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