

Rare Congenital Coagulation Factor Deficiencies: Clinical Manifestations

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ABSTRACT

The clinical symptoms of rare bleeding disorders (RBDs) range from mucosal to life-threatening haemorrhages or functionally restricting haemorrhages. Congenital coagulation factor (F) deficiencies, VII, FX, FXIII, fibrinogen deficiencies and dysfibrinogenaemias, represent 3–5% of all inherited coagulation factor deficiencies. Due to this low prevalence and the variability of bleeding manifestations, the clinical features of these RBDs are not well characterised. For this reason we conducted a retrospective multicentre national survey using patient records to characterize clinical bleeding manifestations in patients with congenital isolated/combined coagulation factor deficiencies or with congenital abnormalities of fibrinogen.

Fifteen departments (11 haematology and four paediatric departments) across Algeria took part in the study, and data from 234 patients were analyzed. The majority of patients (n=164; 70.1%) had isolated congenital coagulation factor deficiencies, the most common of which was FVII deficiency (n=101; 43.2%). Only 221 patients (9.0%) had combined congenital coagulation deficiencies, the most common of which was FVIII/V deficiency (n=13; 5.6%). Congenital fibrinogen abnormalities were reported in 49 patients (20.9%). Overall, there were 327 bleeding episodes in 163 patients. The majority of bleeding episodes (n=195, 59.6%) were in patients with an isolated factor deficiency, the highest incidence of which was recorded for FVII deficient patients (95 bleeds; mean 1.7 bleeds/patient).

Our results support existing descriptions in the literature and may help to target resourcing and plan treatment strategies for those patients at most risk of bleeding.

INTRODUCTION

Rare bleeding disorders (RBDs) include inherited deficiencies of coagulation factor (F) II, FV, FVII, FX, FXIII, fibrinogen deficiencies, and dysfibrinogenaemias, representing 3-5% of all congenital coagulation factor deficiencies [1-4]. RBDs are largely inherited by autosomal recessive

genetics, with an estimated prevalence of homozygous or composite heterozygous mutations ranging from 1/500 000 to 1/2 000 000 individuals [5]. Clinical symptoms range from mucosal to potentially life-threatening haemorrhages (e.g. intracerebral haemorrhage) or functionally restricting haemorrhages (e.g. haematoma or haemarthrosis). Bleeding episodes

are usually secondary to a surgical procedure [6]. Due to the low prevalence rate of RBDs and the variability of bleeding manifestations, they are not well characterized clinically. The aim of this study was to characterize the clinical manifestations of patients with congenital isolated/combined coagulation factor deficiencies or with congenital abnormalities of fibrinogen

MATERIALS AND METHODOLOGIES

We conducted a retrospective, multicentre, national survey using hospital admission and outpatient records between 2000 and 2010 from haematology and paediatric departments in Algeria. Data from patients with FVIII, FIX, or von Willebrand factor deficiencies, or from patients with inherited platelet disorders, were excluded from the study. All patient information retrieved for the study was anonymized at the participating hospitals and the study was conducted in accordance with the Declaration of Helsinki (1996) and the ICH Harmonised Tripartite Guideline for Good Clinical Practice. No local ethics committee approval was required for this study in Algeria.

Using standardized forms, the participating departments provided information on basic patient demographics (gender, age, type of deficiency, coagulation factor level), as well as clinical bleeding manifestations (type of bleeding) and thrombotic events. Descriptive statistics only were used to analyze the data.

RESULTS AND OBSERVATIONS

Fifteen departments (11 haematology and four paediatric departments) across Algeria took part in the study, and data from 234 patients were analyzed. Of these, 51.3% (n=120) were female and 48.7% (n=114) male, and almost all (95.3%; n=223) were ≤ 50 years of age (with 67.9% [n=159] being ≤ 30 years of age). The majority of patients (70.1%; n=164) had isolated congenital coagulation factor deficiencies (FII, FV, FVII, FX, FXI, FXII, or FXIII), the most common of which was FVII deficiency (43.2%; n=101) (Table 1). Only 9.0% (n=21) of patients had combined congenital coagulation deficiencies (FII/V, FII/VII, FVII/V, FVII/X, FVIII/V, FXII/V, or FXIII/V), the most common of which was FVIII/V deficiency (5.6%; n=13). Patients with congenital fibrinogen abnormalities (type I [afibrinogenaemia or hypofibrinogenaemia] or type II

[dysfibrinogenaemia]) accounted for 20.9% (n=49) of all patients.

For patients with FVII deficiency, the majority (57.4%; n=58) had FVII activity levels $>5\%$ (mild factor deficiency), 32.7% (n=33) had levels $>1\text{--}\leq 5\%$ (moderate factor deficiency), and 5.0% (n=5) had levels $\leq 1\%$ (severe factor deficiency); for five patients (5.0%) no information on disease severity was available. Patients with FII or FV deficiency also tended to have mild factor deficiency ($>5\%$ [n=3/4] or $>10\%$ [n=9/17] factor activity levels, respectively). In contrast, patients with FX or FXIII deficiency tended to have severe factor deficiency ($\leq 5\%$ [n=9/15] or $\leq 1\%$ [n=8/10] factor activity levels, respectively), whereas the number of patients with mild FXI or FXII deficiency ($>10\%$ factor activity level; n=7/13 and n=2/4, respectively) was similar to those with severe factor deficiency ($\leq 10\%$ factor activity level; n=6/13 and n=1/4, respectively). Factor activity for patients with combined deficiencies was not consistently recorded and therefore not included in the analyses.

Of the total 234 patients, 71 (30.3%) were asymptomatic (i.e. no bleeding episodes or thrombotic events were recorded); patients with an isolated factor deficiency accounted for more than three-quarters of these (n=58; 24.8% of the overall population or 35.4% of those with isolated factor deficiencies) (Table 1). Of FVII deficient patients, 45 (44.6%) were asymptomatic. Asymptomatic patients comprised nearly half (n=9; 42.9%) of those with combined factor deficiencies, but only a small proportion (n=4; 8.2%) with fibrinogen abnormalities.

Overall, there were 327 bleeding episodes in 163 patients (Table 1). Of these, the majority (59.6% or 195 episodes) were in patients with an isolated factor deficiency (mean 1.8 bleeds/patient). The highest number of episodes were recorded for FVII deficient patients (95 bleeds; mean 1.7 bleeds/patient). For these patients, most bleeding episodes (54/95) were in those with moderate factor VII deficiency ($>1\text{--}\leq 5\%$ factor activity); the most frequent were epistaxis (14 episodes), gingivorrhagia (15 episodes), and menorrhagia (11 episodes). Twenty-nine bleeding episodes occurred in patients with mild FVII deficiency ($>5\%$ factor activity); the most common were menorrhagia (eight episodes), and epistaxis

and gingivorrhagia (four episodes each). In patients with FX deficiency, almost all bleeds (28/32) were in those with severe factor deficiency ($\leq 5\%$ factor activity), most frequently haematoma (nine episodes), haemarthrosis (five episodes), and gingivorrhagia (three episodes).

Among all patients with an isolated deficiency, 106 were symptomatic. Mucocutaneous haemorrhages constituted the majority of bleeding episodes in these patients (115 episodes), followed by haematoma (28 episodes) and haemarthroses (18 episodes).

Table 1: Number of patients and number of bleeding episodes per coagulation factor deficiency type.

	Isolated factor deficiency							Combined factor deficiencies	Afibrinogenaemia	Hypo-fibrinogenaemia	Dys-fibrinogenaemia
	FII	FV	FVII	FX	FXI	FXII	FXIII				
Number of patients, n (%)*	4 (1.7)	17 (7.3)	101 (43.2)	15 (6.4)	13 (5.5)	4 (1.7)	10 (4.3)	21 (9.0)	21 (9.0)	27 (11.5)	1 (0.4)
Number of asymptomatic patients, n (%)*	–	3 (1.3)	45 (19.2)	4 (1.7)	4 (1.7)	1 (0.4)	1 (0.4)	9 (3.8)	2 (0.9)	2 (0.9)	–
Number of symptomatic patients, n (%)*	4 (1.7)	14 (6.0)	56 (23.9)	11 (4.7)	9 (3.8)	3 (1.3)	9 (3.8)	12 (5.1)	19 (8.1)	25 (10.7)	1 (0.4)
Number of bleeding episodes, n (%)†	7 (2.1)	26 (8.0)	95 (29.1)	32 (9.8)	12 (3.7)	3 (0.9)	20 (6.1)	23 (7.0)	59 (18.0)	48 (1.2)	2 (0.6)
Mucocutaneous haemorrhages, n											
Epistaxis	–	3	21	3	1	2	–	1	5	2	–
Gastrointestinal haemorrhage	1	2	5	2	–	–	–	2	1	–	–
Gingivorrhagia	3	9	22	3	2	–	3	6	9	9	1
Haematuria	–	–	–	1	–	–	–	1	1	–	–
Menorrhagia	1	6	20	2	1	1	–	4	4	3	–
Other haemorrhages, n											
Haemarthrosis	1	1	8	6	1	–	1	1	5	3	–
Haematoma	1	2	7	10	1	–	7	4	9	11	–
Haemopericardium	–	–	–	–	–	–	–	1	–	–	–
Haemoperitoneum	–	1	–	1	–	–	1	–	4	–	–
Haemorrhage from loss of milk teeth	–	–	–	1	–	–	–	–	–	–	–
Intracerebral haemorrhage	–	–	2	2	1	–	3	1	7	4	1
Neonatal haemorrhage	–	2	4	1	–	–	4	–	12	6	–
Peripartum haemorrhage	–	–	2	–	1	–	1	–	–	–	–
Post-injury haemorrhage	–	–	2	–	–	–	–	–	2	5	–
Post-operative haemorrhage	–	–	2	–	4	–	–	2	–	5	–
Number of thrombotic events, n	–	1	–	–	–	–	–	–	2	1	–

*Percentage of total number of patients (n = 234); †Percentage of total number of bleeding events (n = 327).

–, no information on episodes recorded/collected.

There were 23 bleeding episodes (7.0% of all bleeds) in patients with combined factor deficiencies (mean 1.9 bleeds/patient); the most commonly reported bleeds were mucocutaneous

haemorrhages (14 episodes) and haematoma (four episodes). In patients with fibrinogen abnormalities, 109 bleeding episodes (33.3% of all bleeds) were recorded (mean 2.4 bleeds/patient);

virtually all (98.2% or 107 episodes) were in patients with a- or hypo-fibrinogenaemia. The most common bleed type in patients with fibrinogen abnormalities was mucocutaneous haemorrhages (35 episodes). For critical bleeding, there were 21 episodes of intracerebral haemorrhage (6.4% of all bleeds) ([Table 1](#)); eight in patients with isolated factor deficiencies (4.1% of bleeds in these patients), one in those with combined factor deficiencies (4.3% of all bleeds in these patients), and 12 in those with fibrinogen abnormalities (11.0% of all bleeds in these patients).

Twenty-nine episodes of neonatal haemorrhage (8.9% of all bleeds) were reported; 11 in patients with isolated factor deficiencies (5.6% of bleeds in these patients) and 18 in those with fibrinogen abnormalities (16.5% of all bleeds in these patients). Two-thirds of the neonatal bleeding episodes in patients with fibrinogen abnormalities were in those with afibrinogenaemia (12 bleeds or 11.0% of all bleeds in patients with fibrinogen abnormalities).

Thrombotic events were uncommon; only four events were reported in 163 patients, one patient with severe FV deficiency, two patients with afibrinogenaemia, and one patient with hypofibrinogenaemia ([Table 1](#)).

Of the 120 females, 73 were aged 21-50 years and 22 were aged 11-20 years. The majority (n=95) had menstrual cycles, of which 33 (34.7%) experienced menorrhagia (a total of 42 episodes), and 24 (25.3%) had ≥ 1 pregnancies. In total, there were 81 pregnancies in 24 women; nearly half of these (38; 46.9%) continued to full term without replacement therapy, and almost one-quarter (19; 23.5%) continued to full term with replacement therapy; 12 (14.8%) women had a termination of their pregnancy prior to 15 weeks. Episodes of peripartum haemorrhages were uncommon (n=4) and only recorded for patients with isolated factor deficiencies (2.1% of all bleeds in these patients) ([Table 1](#)).

DISCUSSION

With this survey we sought to collate and analyze existing information on the clinical manifestations of RBDs. As of 2011, there were 1619 patients with bleeding disorders registered in the official national patient registry in Algeria,

including 1570 with haemophilia and 49 cases of von Willebrand's disease. We further identified 234 patients with RBDs who were not recorded in the registry, representing 12.6% of the total number of patients with bleeding disorders that are currently being followed up in hospitals across Algeria. The observation that only one thrombotic event occurred out of 17 FV-deficient patients (5.9%) suggests a likely genetic variant, specific to Algeria or to the Mediterranean basin. A genetic study to further explore this would be desirable.

The total (1853 patients) currently being followed up is probably still an underestimate, since there is no screening at birth in Algeria and any asymptomatic deficiencies are likely to be missed in general clinical practice. Symptomatic deficiencies are therefore usually diagnosed as a result of follow-up after a clinical manifestation. Consanguinity marriages may be responsible for the apparent higher prevalence of inherited coagulopathies in Algeria compared with previously published figures (12.6% vs. 3-5%). It is worth bearing in mind that this study was a retrospective survey of patients' hospital records, and as such, the level and accuracy of the information provided varied.

The classification of RBDs disease severity has recently been updated from that utilized in the current study [\[4\]](#). Under these new criteria, all of the FVII deficient patients classified here as moderate would be reclassified as severe (<10% factor activity), and many classified as mild FVII deficiency would be reclassified as severe or moderate (<10-20% factor activity). This may explain the observation reported here of bleeding in patients classified as mild/moderate FVII deficiency, and suggests that the suggested reclassification [\[4\]](#) is warranted,

CONCLUSION

The clinical manifestations of RBD reported here are broadly consistent with the existing descriptions in the literature [\[1, 3, 5, 6\]](#). These findings may be useful in helping to plan therapeutic strategies for patients most at risk of bleeding episodes.

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DISCLOSURES

The authors have no competing interests.

LIST OF ABBREVIATIONS

RBD – Rare bleeding disorders

F – Factor



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