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Case report

Déficit combiné en facteurs V et VIII : étude d'une fratrie de quatre enfants

Combined Factor V and Factor VIII Deficiency: A Case Series of Four Siblings from a Consanguineous Family

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RÉSUMÉ

Introduction : Le déficit combiné en facteurs V et VIII (F5F8D) est une coagulopathie héréditaire rare, de transmission autosomique récessive, caractérisée par une diminution simultanée de l'activité des facteurs V (FV) et VIII (FVIII). Sa prévalence est estimée à 1/1 000 000, mais elle est plus fréquente dans les régions à forte consanguinité. **Objectifs** : Rapporter les données cliniques et biologiques d'une fratrie de quatre enfants atteints de F5F8D, issus d'un mariage consanguin de premier degré, et discuter les particularités diagnostiques et thérapeutiques de cette entité. **Méthodes** : Les quatre enfants (trois garçons, une fille, âgés de 11 à 32 ans) et leurs parents ont bénéficié d'un bilan d'hémostase standard (taux de prothrombine [TP], temps de céphaline activé [TCA], fibrinogène) et d'un dosage fonctionnel des facteurs de coagulation sur automate STA Compact MAX2. **Résultats** : Tous les enfants présentaient un TP bas et un TCA allongé, avec des taux de FV et de FVIII compris entre 17 % et 33 % (valeurs normales : 70 140 % pour le FV, 60 150 % pour le FVIII). Les autres facteurs (II, VII, X, fibrinogène) étaient normaux. Les deux parents avaient un profil de coagulation normal, confirmant le mode récessif. Les manifestations hémorragiques étaient modérées (épistaxis, ecchymoses post traumatiques). **Conclusion** : Cette observation illustre la présence d'un F5F8D chez les quatre enfants d'une même fratrie, soulignant l'importance d'un bilan familial systématique en cas de consanguinité. L'absence de test génétique constitue une limitation, mais le diagnostic biologique couplé à l'enquête familiale permet une prise en charge adaptée et un conseil génétique approprié.

MOTS CLES : Déficit combiné en facteurs V et VIII, F5F8D, consanguinité, coagulopathie rare, hémostase.

ABSTRACT

Introduction: Combined factor V and factor VIII deficiency (F5F8D) is a rare autosomal recessive bleeding disorder characterized by concomitantly decreased activity of factors V (FV) and VIII (FVIII). Its prevalence is estimated at 1/1,000,000 but is higher in regions with high consanguinity rates. **Objectives**: To report the clinical and laboratory data of a sibling group of four children with F5F8D born to first-degree consanguineous parents and to discuss the diagnostic and therapeutic particularities of this entity. **Methods**: The four children (three males, one female, aged 11–32years) and their parents underwent standard hemostasis tests (prothrombin time [PT], activated partial thromboplastin time [aPTT], fibrinogen) and functional coagulation factor assays using the STA Compact MAX2 automated system.

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Results: All children showed decreased PT and prolonged aPTT, with FV and FVIII levels ranging from 17 % to 33 % (normal ranges: 70-140 % for FV, 60-150 % for FVIII). Other factors (II, VII, X, fibrinogène) were normal. Both parents had normal coagulation profiles, confirming the recessive inheritance. Bleeding manifestations were mild to moderate (epistaxis, post-traumatic ecchymoses). **Conclusion**: This case series demonstrates F5F8D in all four siblings of a single family, highlighting the importance of systematic family screening in consanguineous settings. The lack of genetic testing is a limitation, but biological diagnosis combined with family investigation allows for appropriate management and genetic counseling.

KEYWORDS: Combined factor V and VIII deficiency, F5F8D, consanguinity, rare coagulopathy, and hemostasis.

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1. Introduction

Combined factor V and factor VIII deficiency (F5F8D, OMIM 227300) was first described in 1954 [1]. It is a rare hereditary coagulopathy that accounts for approximately 3 % of all congenital bleeding disorders [2]. The bleeding phenotype is generally mild to moderate [3]. The disease has an estimated prevalence of 1:1 000 000 in the general population, but its frequency is significantly higher in regions where consanguineous marriages are common, such as the Middle East, Mediterranean basin, and South Asia [4].
The molecular basis of F5F8D involves mutations in one of two genes: LMAN1 (located on chromosome 18q21) or MCFD2 (on chromosome 2p21) [5, 6]. These genes encode proteins that form a cargo receptor complex essential for the intracellular transport of both FV and FVIII from the endoplasmic reticulum to the Golgi apparatus [7]. Consequently, mutations in either gene lead to a simultaneous decrease in the secretion of both factors, resulting in plasma activity levels typically between 5 % and 30 % of normal [8].

The diagnosis is suspected when both the prothrombin time (PT) and activated partial thromboplastin time (aPTT) are prolonged [3, 9]. Management relies on replacement therapy with fresh frozen plasma (FFP), desmopressin (DDAVP), or plasma derived or recombinant factor concentrates [8].
We report a family of four children (three males, one female) born to first degree consanguineous parents, all of whom were diagnosed with F5F8D following a preoperative hemostasis work up in the youngest sibling.

2. Case Presentation

The family consists of four siblings (three males, one female) born to a first degree consanguineous marriage. The children's ages are 11 (GC), 27 (GN), 30 (GI), and 32 (GD) years. The propositus (GN) was identified during a preoperative assessment for elective surgery.

2.1. Index Case (GN, 27 year old male)

Routine preoperative coagulation screening revealed a decreased PT (49 %) and prolonged aPTT (ratio 1.9). Further functional coagulation factor assays showed decreased levels of FV (21 %) and FVIII (17 %), while other factors (II, VII, X, fibrinogen) were within normal ranges (Table 1). The patient reported a history of childhood epistaxis and easy bruising after minor trauma.

2.2. Family Screening

Given the findings in the index case and the history of consanguinity, a full family hemostasis work up was performed. All siblings underwent standard tests (PT, aPTT, fibrinogen) and functional factor assays using the STA Compact automated system. The results are summarized in **Table 1.**

All four siblings exhibited prolonged PT and aPTT, with concomitant decreases in FV (range 17–28 %) and FVIII (range 17–33 %). The levels of other coagulation factors were normal. Both parents had entirely normal coagulation profiles, consistent with heterozygous carrier status.

2.3. Clinical Bleeding Phenotype

All siblings reported a history of mild bleeding symptoms: episodic childhood epistaxis and easy bruising after minor trauma. No patient had experienced spontaneous joint bleeding, gastrointestinal hemorrhage, or intracranial bleeding

3. Discussion

This case series describes a family in which all four children born to first degree consanguineous parents were diagnosed with F5F8D. The laboratory findings simultaneous prolongation of PT and aPTT with isolated reductions in FV and FVIII activities are classic for this disorder [3, 9]. The factor levels observed (FV 17–28 %, FVIII 17–33 %) fall within the

typical range of 5–30 % reported in the literature [8]. The normal coagulation profiles of the parents confirm the autosomal recessive inheritance pattern.

The clinical phenotype in our patients is consistent with the generally mild to moderate bleeding tendency described in F5F8D [3, 4]. The most common manifestations in published series include epistaxis, menorrhagia, and excessive bleeding after surgery or trauma. Our patients reported only episodic epistaxis and easy bruising, and three siblings were diagnosed incidentally through family screening. This underscores that F5F8D may remain asymptomatic or paucisymptomatic for years, only being detected during hemostasis testing prompted by unrelated reasons.

From a pathophysiological perspective, F5F8D is caused by mutations in either the LMAN1 or MCFD2 gene, which encode components of a cargo receptor complex essential for the endoplasmic reticulum to Golgi transport of both FV and FVIII [5-7]. In our family, genetic testing was not performed due to limited resources, which is a recognized limitation. Such testing would have identified the causative mutation and allowed for precise genetic counseling.

The management of F5F8D is based on replacing the deficient factors. For bleeding episodes or surgical prophylaxis, therapeutic options include fresh frozen plasma (FFP), desmopressin (DDAVP), and plasma-derived or recombinant factor concentrates [8]. In our patients, no acute bleeding required intervention at the time of diagnosis, but all were advised to avoid NSAIDs and to seek hemostatic evaluation before any invasive procedure.

This case series highlights several important points for clinical practice:

1. **Systematic family screening** is crucial in consanguineous families when a hereditary coagulopathy is identified.
2. **F5F8D should be considered** in any patient with decreased PT and prolonged aPTT, even in the absence of severe bleeding symptoms.
3. **Genetic counseling** is essential for families with autosomal recessive disorders, especially in communities where consanguinity is common.

The main limitation of this report is the absence of genetic confirmation. Nevertheless, the consistent biological phenotype across all four siblings, coupled with the normal parental profiles, strongly supports the diagnosis of F5F8D.

4. Conclusion

We report a family in which all four children born to first degree consanguineous parents were diagnosed with combined factor V and factor VIII deficiency. The cases illustrate the classic laboratory profile of simultaneous prolongation of PT and aPTT with isolated reductions in FV and FVIII activities, and a mild bleeding phenotype. This observation reinforces the importance of family screening in consanguineous settings and underscores the need for increased awareness of this rare coagulopathy among clinicians and laboratory specialists. Although genetic testing was not available in this instance, biological diagnosis combined with family investigation allows for appropriate management, preventive measures, and informed genetic counseling.

5. Conflicts of interest

The authors declare no conflict of interest.

6. References

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Table 1. Hemostatic profile of the family members

Subject (age, sex)	PT (%)	aPTT ratio	Fibrinogen (g/L)	FII (%)	FV (%)	FVII (%)	FX (%)	FVIII (%)
Normal ranges	70-100	<1.2	1.5-3.5	70-140	**70-140**	70-140	70-140	**60-150**
Father (GM)	100	1.03	4.15	134	157	140	140	176
Mother (AN)	98	1.00	2.5	110	118	119	100	120
Child 1 (GD, 32 F)	46	1.5	2.8	121	**17**	132	129	**18**
Child 2 (GN, 27 M)	49	1.9	2.68	120	**21**	103	112	**17**
Child 3 (GI, 30 M)	58	2.05	3.9	138	**28**	105	118	**33**
Child 4 (GC, 11 M)	47	1.6	3.4	142	**19**	98	106	**22**