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Combined Deficiency of Coagulation Factors V and Viii about 4 Cases of the Same Family

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Abstract: The combined deficiency of factor V and factor VIII (F5F8D) has been described since 1954 as a rare congenital disorder, responsible of variable intensity hemorrhagic syndromes oftenly moderate. It is an autosomal recessive bleeding caused by mutations in genes encoding two proteins LMAN1 and MCFD2, involved in the passage of FV and FVIII between the endoplasmic reticulum and the Golgi apparatus before their secretion. Our work's aims are to make known this rarely diagnosed pathology, by providing the recent data from the literature and to sensitize the practitioners to seek the presence of a F5F8D in front of a simultaneous prolongation of the activated partial thromboplastin time (APTT) and the prothrombin time (PT) Our patients have moderate hemorrhagic syndrome dominated by epistaxis, gingivorrhagia, bleeding after dental extraction, surgery or injury, and menorrhagia. The results revealed prolonged activated partial thromboplastin time and prothrombin time. Plasma levels of FV and FVIII were between 11% and 18%, the other factors were normal. The F5F8D diagnosis was retained after several checks. The discovery of these 4 cases prompted us to extend the investigation toward the rest of the siblings and the offspring but the results were normal.
Keywords: Combined deficiency - Facteur V - Facteur VIII - LMAN1 - MCFD2.

INTRODUCTION

The combined deficiency of factor V and factor VIII is a hereditary disorder of coagulation, autosomal, recessive and rare, it is observed in regions of strong consanguinity [1].

It is characterized by the concomitant decrease of the plasma concentrations of the two factors V and VIII despite their synthesis which is coded by two different genes.

Hemorrhagic complications are mild or moderate, but require compensation for the double deficiency of FV and FVIII, in the form of fresh frozen plasma (FFP) for FV and desmopressin or FVIII concentrate for the other factor.

OBJECTIVES OF THE STUDY

To make known this rare disease, by reporting four Moroccan cases of combined deficiency in FV and FVIII in the same family, diagnosed in the Hematology Department of the Military Hospital Avicenna of Marrakech.

PATIENTS AND METHODS

The study reports the observation on a sample of 4 patients hospitalized at Avicenna Military Hospital. After the discovery of the first case, we decided to expand our investigations to all the siblings and their descendants with a total of 18 people.

This anomaly was discovered in our patients following an exploration of the first-line coagulation assessment: the prothrombin time (PT), activated partial thromboplastin time (APTT), with calculation of the Rosner index (IR). IR = [(TCA Mixture - TCA Control) / TCA Patient)] x 100 when it is less than 15% means the factor deficiency.

Secondly, the determination of coagulation factors in case of TCA correction (IR ≤ 12%). These tests are performed by automated chronometric method respecting the pre-analytical phase and confirmed on a second sample.

RESULTS

Epidemiological study

In our series all patients are adults with an average age of 56.25 ± 8.05, with a sex ratio = 1.

Clinical discovery circumstances

Case N ° 1 (index): This is a 45-year-old woman born to parents of second degree consanguinity. It was sent to us for an investigation of an increase in Activated Partial Thromboplastin Time (APTT) and Quick Time (TQ) requested in the context of a preoperative assessment associated with hemorrhagic manifestations. Case N ° 2: He is a 59-year-old man with repeated epistaxis since he was 15 years old.

He also had bleeding during a tooth extraction that required hospitalization for transfusion, and hematoma of the right thigh after trauma that required surgical drainage two years ago. The patient reported the notion of repeated gingivorrhages without other manifestations including no hemarthrosis or haemorrhage during circumcision.

Case 3

This is a 64-year-old man who had bleeding after tooth extraction which required a blood transfusion 5 years ago. He also reported the presence of a spontaneous epistaxis repeated since childhood and gingivorragies. Case 4: A 57-year-old woman with a history of delivery bleeding in 4 deliveries required blood transfusions, associated with bleeding during tooth extractions, prolonged post-traumatic bleeding, and spontaneous gingivorrhagia.

Biology report

All assessments performed in our patients showed a simultaneous lengthening of the PT and the APTT with a low prothrombin rate, fibrinogen level and bleeding time were normal (Table I).

The antigenic activity and co-factor activity of von Willebrand factor ristocetin in our patients was normal (Table II).

Table-I: Assessment of hemostasis in our patients

Analysis	Results				
Patients	Case (index)	Case 2	Case 3	Case 4	Normal Values
PT	22,8	18,30	20,02	19,4	12,9 (secondes)
APPT	101,1	86	86	78,7	26 à 42 (secondes)
Fibrinogen	3,52	2,83	3,29	2,35	2 à 4 g/l
TS	4	3	4	2	2 à 10 (minutes)

Table-II: Assay of antigen activity and cofactor activity of von Willebrand factor ristocetin

analysis	Résults				
	Case (index)	Case 2	Case 3	Case 4	Normal values
Fvw, Ag	78%	83%	69%	96%	50- 160%
Fvw, CoR	75%	70%	102%	90%	50-150%

The determination of coagulation factors in patients showed a combined factor V and factor VIII deficiency, the other factors were normal (Table III).

Cell blood count and liver function tests were requested in all patients in our series were without abnormalities. The family tree: Figure 1

Table-III: Determination of factor V, VIII in our patients

analysis	Résults				
	Cas (index)	Cas 2	Cas 3	Cas 4	normal values
Factor V	11	13	13	16	70- 120%
Factor VIII	16	16	14	18	60-150%

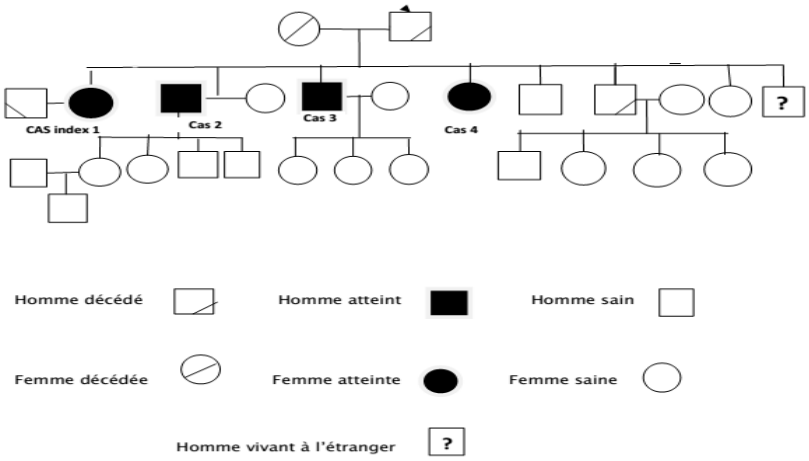

Fig-1: family tree of the family

DISCUSSION

The combined factor V and VIII deficiency is a rare disease whose prevalence is estimated to be between 1/ 100,000 and 1 / 1,000,000 depending on the region, more common in high consanguinity populations such as the Middle East Sephardic Jews and populations around the Mediterranean basin [2-4]. In Morocco the revalence of this pathology is still unknown.

The combined factor V and VIII deficiency affects both men and women (sex ratio = 1) [5, 6]. Clinically, the combined factor V and VIII deficiency is manifested by a haemorrhagic syndrome with variable intensity [7]. In all studies, the blood balance sheets deficient patients had a simultaneous lengthening of PT and APTT, and low plasma levels of both factors V and usually VIII between 5 and 30% of normal, by against the CBC, fibrinogen, bleeding time and von Willebrand factor were normal [8].

Parahemophilia associated with type 1 von Willebrand disease may also be a decrease in FV and FVIII levels due to the indirect effect of von Willebrand factor on FVIII stability [8]. Although the coincidence of Parahemophilia and Hemophilia A is a rare possibility, because of the low prevalence in the general population (1 / 1,000,000 for parahemophilia and 1 / 5,000 for men for Hemophilia A).

The ultimate confirmation of DF5F8 comes from the identification of LMAN1 (lectin mannose binding 1) and MCFD2 (Multiple Coagulation Factor Deficiency 2) mutations, however no routine genetic testing is currently available for DF5F8.

The mutation analysis is performed on a research basis in several medical centers, but in all cases the clinical management of DF5F8 is not based on molecular diagnosis. The mutations LMAN1 (lectin mannose binding 1) and MCFD2 (Multiple Coagulation Factor Deficiency 2) are present in all cases of (DF5F8), in the form of insertion/deletion mutations, nonsense and regulatory site mutations that completely abolish the protein function [9-11].

The genetic study in our patients was not done because of the high cost and the long duration for the demonstration of the mutations responsible for the combined factor V and VIII deficiency. The treatment of bleeding episodes depends on the severity of bleeding and the plasma levels of factors V and VIII [5].

The use of fresh frozen plasma with recombinant factor VIII a allows the correction of this disorder. Desmopressin may increase the rate of FVIII in a patient with a mild deficit [12].

CONCLUSION

The combined factor V and factor VIII deficiency is a rare hereditary disease, Morocco is part of the Mediterranean basin concerned by this deficit, hence the need to suspect this abnormality in all patients with hemorrhagic syndrome, a simultaneous lengthening of the PT and APPT with or without a family history of consanguinity.

For this reason the FV assay must be performed for any moderate FVIII deficiency in order to search for the combined deficit.

Conflicts of interest

The authors do not declare any conflict of interest

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