Discovery of Type 3 von Willebrand Disease in a Cohort of Patients with Suspected Hemophilia A in Côte d'Ivoire

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Original Article

Discovery of Type 3 von Willebrand Disease in a Cohort of Patients with Suspected Hemophilia A in Côte d'Ivoire

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Abstract. ***Background:*** **Type 3 von Willebrand disease (VWD) is the most severe form of VWD, characterized by a near-total absence of von Willebrand factor (vWF), leading to a massive deficiency in plasmatic factor VIII (FVIII). VWD may be confused with hemophilia A, sometimes leading to misdiagnosis. The purpose of this work was to finalize the biological diagnosis of patients with FVIII activity deficiency in Abidjan in order to guide the best type of management.**
Methods: **We conducted a cross-sectional descriptive study from June 2018 to April 2019. Forty-nine patients, all of whom had lower FVIII levels or had been referred for a bleeding disorder, were monitored in the clinical hematology service. The pro-coagulant activity of coagulation factors was performed in Abidjan. The assays for von Willebrand antigen and activity were performed at Nîmes University Hospital in France.**
Results: **The mean age of patients was 13.8 years (1 – 65) and 86% were Ivorian. FVIII deficiency was discovered during a biological checkup, circumcision or post-traumatic bleeding, in 33%, 31% and 29% respectively. The FVIII deficiency of patients was classified as severe (89.8%), moderate (8.2%) and mild (2%). Only one patient had a quantitative deficiency of von Willebrand factor (vWF: Ag <3%) with undetectable von Willebrand factor activity (vWF: Ac) and an FVIII level <1%.**
Conclusions: **Not all of the congenital deficiency of FVIII are represented by hemophilia A. It was crucial to assess the Willebrand factor of these patients followed in Côte d'Ivoire for whom hemophilia A had been suspected.**

Keywords: von Willebrand type 3; Hemophilia A; Côte d'Ivoire.

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Introduction. Hemophilia is an X-linked recessive disease and is the second most common hereditary

hemorrhagic disease after von Willebrand disease (VWD). It almost exclusively affects males with an average incidence of approximately one in 5,000 births for hemophilia A (HA) which is defined by a deficiency in coagulation factor VIII (FVIII), and one in 20,000 to 30,000 births for hemophilia B (HB) which is defined by a deficiency in factor IX (FIX).[1] These deficiencies result from mutations in the genes encoding for FVIII or FIX.

VWD is an inherited bleeding disorder caused by a mutation in the gene encoding the von Willebrand factor (vWF), located on the autosomal chromosome 12.[2] VWD is classified into 3 main types. Type 1 VWD is a partial quantitative deficiency, Type 2 is a qualitative defect subdivided into 4 subtypes (2A, 2B, 2M and 2N) and Type 3, the least common but most serious form, is a complete deficiency of Vwf.[3,4] It has an estimated prevalence of 0.5 to 1 per million in western countries and may be more prevalent in communities with high consanguinity.[5,6]

FVIII is chaperoned by the vWF in the blood to protect it from proteolysis, especially by the activated C protein. Any significant change in vWF is usually accompanied by a parallel variation in the level of FVIII in the bloodstream.[7] Therefore, FVIII decrease is found both in HA and VWD. In Type 3 VWD, the level of FVIII is significantly reduced, and therefore Type 3 VWD may be confused with severe HA. In addition to cutaneous and mucous membrane bleeding, which are characteristic of primary hemostasis disorders, hemarthrosis and hematomas which are characteristic of coagulation disorder, may also occur. These features may lead to misdiagnosis.

The aim of this work was to improve the biological diagnosis of patients with FVIII deficiency monitored in the clinical hematology department of Yopougon University Hospital in Abidjan, in order to improve the standard of care for these patients.

Patients and Methods.

Patients. The 49 patients under study had been referred for therapeutic management of a hemorrhagic disease associated with a reduction of FVIII-dependent procoagulant plasma activity, called FVIII: C deficiency. They came from different families and were monitored in the clinical hematology department, or referred for coagulation disorder. All patients had been contacted by telephone to arrange an appointment to inform them of the study and obtain their written, informed consent. For children, consent was collected from a family member.

Methods. This is a cross-sectional descriptive study conducted from June 2018 to April 2019. Some of the tests, i.e. the coagulation factor assays, were performed at the central laboratory of Yopougon University Hospital in Abidjan. The rest (vWF analysis) was performed at the Hematology Laboratory of Nîmes University Hospital, France. The blood was collected by the least traumatic venipuncture as possible, on citrated anticoagulant, 9 volumes to 1. Citrated plasmas poor in platelets were prepared by double centrifugation at 2 500 rpm for 10 minutes, then aliquoted and frozen to -80 °C before being shipped to France on dry ice.

Factor assay. Factors and activities were measured by a one-stage assay on a semi-automatic coagulometer by chronometric technique. We used a kit consisting of human plasma immunodepleted of FVIII and a ready-to-use APTT reagent and calcium chloride (0.020 mol/l). The factor level was determined via a calibration line made of calibrated control plasmas. The admissibility of the assay procedure was validated by control plasmas.

Phenotype of von Willebrand factor. The vWF analysis was performed on a fully automatic coagulation analyzer.

Functional determination of von Willebrand factor: vWF: Ac. vWF activity of patient plasma was determined using the reagent, which uses polystyrene particles coated with a recombinant platelet protein (Glycoprotein Ib, rGPIb) with two «function gain» mutations allowing binding of the Willebrand factor in the absence of ristocetin. vWF in the plasma then spontaneously recognizes rGPIb and induces the agglutination of polystyrene particles. Agglutination is measured by turbidimetry.

*Von Willebrand factor antigen: vWF: Ag***.** Quantitative determination of plasma vWF was carried out by a technique based on specific polyclonal antibodies. This was, therefore, an assay for the vWF antigen (vWF: Ag) using an immuno-turbidimetric technique.

Results.

Epidemiological and clinical characteristics. During the study period, the 49 patients included children and adults aged 4 months to 65 years, with an average age of 13.8 years. The majority were children (67%, **Table 1**). We registered 42 patients of Ivorian nationality (86%). The decrease in procoagulant factor VIII level was found either during a biological survey of the family, during circumcision or post-traumatic bleeding in 33%, 31% and 29% of cases, respectively (**Table 2**). The clinical signs were dominated by the association of hematomas, hemarthrosis, and bleeding from mucous membranes (69%).

Biological data. In this study, factor VIII deficiency was classified as severe (less than 1% residual activity), moderate (1 to 5%), and mild (6 to 40%) respectively

Table 1. Classification of patients by age group.

Age groups (Years)	Frequency	Percentage
[0 – 5]	10	20.4%
[5 – 10]	16	32.6%
[10 – 15]	7	14.3%
[15 – 25]	9	18.4%
[25 – 65]	7	14.3%
Total	**49**	**100%**

Mean: 13.8 years; min = 4 months; max= 65 years.

Table 2. Circumstances of discovery of the disease.

Circumstances of discovery	Frequency	Percentage
Family survey	16	32.6%
Circumcision	15	30.6%
Bleeding after trauma	14	28.6%
Hematomas	4	8.2%
Total	**49**	**100%**

in 89.8%, 8.2% and 2% of cases (**Table 3**). vWF antigen and activity levels were found to be deficient in one patient. 71.4% and 87.8% of patients had normal antigen and activity levels, respectively (**Table 4**). The patient with vWF deficiency had less than 3% vWF: Ag and an undetectable vWF: Ac, with a FVIII level of less than 1% (**Table 5**).

Discussion. This study allowed us, for the first time, to evaluate vWF in patients with low levels of factor VIII (anti-hemophilic factor A), suggesting hemophilia A. There has been little research on hemophilia and von Willebrand disease in sub-Saharan African countries,[8,9,10] particularly in the Côte d'Ivoire. The World Federation of Hemophilia Report on the Annual Global Survey reported 96 cases of hemophilia in 2018, including 83 hemophiliacs A and 13 hemophiliacs B in our country with 25,069,229 inhabitants.[11]

More than half of the study population consisted of children under 15 years of age. The management of patients with bleeding disorders in our country has evolved considerably over the last four years, thanks to the World Federation of Hemophiliacs (WFH). This progress in clinical and laboratory diagnosis has led to the registration of new patients, including many children whose disease was discovered following recent circumcision or a family survey. In the Côte d'Ivoire, circumcision is practiced during childhood, which explains the high number of children in our study. Early diagnosis of hemostasis disorders such as hemophilia and VWD is very important in order to prevent bleeding and death caused by circumcision and other trauma.[12] These two causes of bleeding represent 31% and 29% of cases, respectively. In Africa, circumcision is the most common surgical procedure for young boys, mainly for religious, cultural and social reasons.[13]

Table 3. Factor VIII level by age

	Factor VIII level (FVIII : C)				
Age class (Years)	**< 1**	**[1-5]**	**[6-40]**	**Frequency**	**Percentage**
[0 – 5]	10	0	0	10	20.4%
[5 – 10]	15	1	0	16	32.7%
[10 – 15]	6	1	0	7	14.3%
[15 – 25]	9	0	0	9	18.4%
[25 – 65]	4	2	1	7	14.3%
Total	**44 (89.8%)**	**4 (8.2%)**	**1 (2%)**	**49 (100%)**	

Table 4. vWF Quantitative (vWF: Ag) and Functional (vWF: Ac) Assays.

vWF level (%)	vWF:Ag		vWF: Ac	
	Frequency	**Percentage**	**Frequency**	**Percentage**
[0-40]	1	2.0%	1	2%
[40-150]	35	71.4%	43	87.8%
[150-300]	13	26.6%	5	10.2%
Total	**49**	**100%**	**49**	**100%**

Table 5. Results of the FVIII, vWF: Ag and vWF: Ac assays for each patient.

Codes	Age	FVIII (%)	vWF : Ag (%)	vWF : Ac (%)
1	16 Years	< 1	72	80
2	12 Years	<1	126	118
3	14 Years	1.3	138	95
5	17 Years	<1	102	79
6	65 Years	14.4	134	91
7	29 Years	<1	71	48
8	31 Years	<1	165	128
10	6 Years	<1	166	119
13	25 Years	<1	106	85
14	24 Years	<1	87	64
15	10 Years	<1	183	113
17	32 Years	<1	126	83
18	10 Years	<1	75	52
20	7 Years	<1	114	109
21	4 Years	<1	71	66
23	20 Years	<1	106	74
24	10 Years	<1	102	73
25	3 Years	<1	89	66
27	19 Years	<1	90	73
28	13 Years	<1	137	160
30	9 Years	<1	144	98
31	12 Years	<1	158	160
32	15 Years	<1	135	119
33	1 Year	<1	148	126
34	8 Years	<1	162	160
37	18 Years	<1	161	145
38	21 Years	<1	97	66
39	26 Years	<1	241	160
40	22 Years	<1	58	52
41	9 Years	<1	278	175
42	8 Years	<1	100	65
43	9 Years	<1	116	102
44	11 Years	<1	127	123
45	2 Years	<1	145	109
46	10 Years	<1	43	41
47	20 Years	<1	84	63
48	7 Years	<1	162	140
49	5 Years	<1	202	141
50	6 Years	2,6	103	86
51	6 Years	<1	98	84
52	34 Years	1.4	171	96
53	28 Years	2.4	173	128
55	5 Years	<1	90	85
56	3 Years	<1	92	88
60	**4 months**	**<1**	**<3**	**0**
61	2 Years	<1	167	139
62	14 Years	<1	138	66
64	8 Years	<1	79	68
66	2 Years	<1	135	92

Severe factor VIII deficiency largely predominates, 90% compared with just 8% and 2% of moderate and mild deficiency, respectively. Our results differ from those obtained by Diop et al. in Senegal, who found a predominance of moderate forms (56%) versus only 30% of severe forms.[14] Congenital deficiency in FVIII instinctively leads to hemophilia A. But a plasma decrease in FVIII can also be observed with abnormality of its carrier protein, the von Willebrand factor. Evaluation of vWF by antigen assay and functional activity allowed us to identify one patient with severe FVIII deficiency associated with absent VWF. This 4-month-old child had been referred to the department for an isolated prolongation of activated partial thromboplastin time. This study ultimately allowed us to diagnose Type 3 von Willebrand disease

in the patient. In this particular case, the hemorrhagic phenotype depended both on the level of vWF and the level of FVIII.[15,16,17] Several similar cases of patients with Type 3 von Willebrand disease misdiagnosed as having hemophilia A have been described in the literature.[18,19,20,21] The prevalence of Type 3 von Willebrand disease is very low, ranging from 0.1 to 5.3 per million inhabitants and varies considerably from one region of the world to another, with increased prevalence in areas where consanguineous marriages are more common.[22,23] The highest rate is observed among Arabs and the lowest in southern Europe.[24] The case described in our study is of Arab origin, where consanguineous marriages are common.[25,26,27]

Misdiagnosis of VWD leads to disparate and inadequate treatment. The therapy in Type 3 VWD aims to correct the combined defects of primary and secondary hemostasis. This requires restoring a satisfactory level of circulating vWF which, by stabilizing FVIII, will erase its secondary deficit and then be accompanied by its reappearance in the plasma. The basic treatment for Type 3 von Willebrand disease is a substitution treatment with vWF concentrates of plasmatic or recombinant origin. For example, if there is time to prevent hemorrhage during a programmed surgery, these concentrates will induce the delayed reappearance of FVIII. If urgent treatment is required (for example crucial to treat acute hemorrhage), then vWF and FVIII should be given. Type 3 von Willebrand disease patients do not respond to desmopressin,[28,29,30] and this treatment is not recommended. However, there are some discordant data about this therapeutic option.[16]

Conclusions. Our work highlights the importance of evaluating vWF in patients diagnosed with factor VIII deficiency and for whom hemophilia A is suspected. Not all FVIII deficits, however severe, are hemophilic A. The clinical relevance of the treatment depends on complete phenotyping.

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