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Co-existing mild Haemophilia A with Mild Type 1 Von Willebrand Disease: Case Report

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ABSTRACT

Von Willebrand disease and haemophilia A are the two most common inherited bleeding disorders. Despite the relatively high frequency of those two bleeding disorders in the general population, reports of their coexistence together or of combined coagulopathies in general are rare. We describe a 1-year-old male with confirmed mild haemophilia A co-existing with mild type 1 VWD. The 1- year old male was admitted to our hospital with a history of excessive bleeding following circumcision. Initial laboratory evaluation revealed a prolonged activated partial thromboplastin time (APTT) of 46.2 s (normal range 23.2-34.7), and low FVIII activity level of 5.5% of normal. His subsequent evaluation, was also consistent with mild type 1 VWD with a decreased VWF antigen (VWF:Ag) of 50%, decreased ristocetin cofactor activity (VWF:RCo) of 44%. The DNA testing detected a C2 domain R2304H mutation of the FVIII gene.

We believe that the co-existence of VWD and haemophilia A is underappreciated, under-diagnosed, and under-reported.

Keywords: Haemophilia, Von Willebrand disease

ÖZET

Hafif Tip von Willebrand Hastalığı ile Hafif Hemofili A Birlikteliği

Von Willebrand hastalığı (VWH) ve Hemofili-A (HA) en yaygın iki kalıtsal kanama bozukluğudur. Genel populasyonda bu iki kanama bozukluğunun nispeten sık görünmelerine rağmen birbirleriyle birlikte seyretmeleri nadir olarak rapor edilmektedir. Bir yaşında erkekte hafif tip 1 VWH ile hafif hemofili-A birlikteliğini tanımladık. Bir yaşında erkek sünnet sonrası aşırı kanama ile hastaneye başvurdu. Başlangıç laboratuvar değerlerinde uzun aktive partial thromboplastin zamanı 46.2 sn (normal deger 23.2-34.7), FVIII aktivitesi 5.5%, von Willebrand Factor antigen düzeyi 50%, von Willebrand Factor ristosetin kofactor aktivitesi 44% olarak bulundu. DNA analizinde FVIII geninde C2 domain R2304H mutasyonu bulundu.

Von Willebrand hastalığı ve Hemofili- A birlikteliğinin tahmin edilenden daha az teşhis ve bildirildiğine inanıyoruz.

Anahtar Kelimeler: Hemofili, Von Willebrand hastalığı

Table1. Von Willebrand disease and Haemophilia- A laboratory data

	Normal range	Father	Mother	Child
FVIII: C	50-150%	43	25	5.5
vWF: Ag	60-150%	61	77	50
vWF: Rco	60-150%	62	79	44
vWF: CB	60-150%	51.5	85.7	55
FVIIIc/vWF: Ag ratio	1.2-1.7	0.70	0.32	0.12
vWF: RCo/vWF: Ag ratio	0.7-1	1.02	1.03	0.88
vWF: CB/vWF: Ag		0.84	1.11	1.10
vWF-FVIII binding assay		0.99	0.87	1.00
vWF: multimeric composition		normal	normal	normal
Genetic Analysis of FVIII Gene		none found	Factor VIII C2 domain R2304H mutation	Factor VIII C2 domain R2304H mutation

co-existing with mild type 1 VWD. Combined inherited coagulopathies coexisting with VWD are not uncommon and frequently are phenotypically divergent from classical VWD. Haemophilia A is the most common congenital coagulopathy to coexist with VWD.[5] Casonato et al. reported one case of haemophilia A associated with VWD type 2N (6) and another case in which mild VWD type 1 coexisted with severe haemophilia A.[7] The remainder of the cohort had VWD type 1 associated with haemophilia A, and their clinical courses were notable for the predominance of mucocutaneous bleeding and severe haematuria, rather than intramuscular and intraarticular bleeds characteristic of haemophilia.[8,9] The diagnosis of this combined deficiency state was suspected either because of their known family medical histories of coagulopathies, or the unusual pattern of their bleeding complications. Another clue was the presence of an abnormally prolonged bleeding time.[10]

In Turkey, where approximately 100% of boys undergo circumcision, APTT is rarely checked before circumcision and mild prolonged APTT are generally thought to be a result of a technical problem. Bleeding following circumcision becomes an important clue for the patients with mild haemophilia, for the male who is the first son in the family. The likelihood of co-existing coagulopathies should increase in populations where consangineous marriages are common. We believe that the co-existence of VWD and haemophilia A is underappreciated, under-diagnosed, and under-reported because these are the two most commonly inherited coagulopathies.

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REFERENCES

1. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood 69: 454-9, 1987.
2. Sadler JE. von Willebrand disease type 1: a diagnosis in search of a disease. Blood 101: 2089-2093, 2003.
3. Favaloro EJ, Bonar R, Kershaw G, et al. Reducing errors in identification of von Willebrand disease: The experience of the Royal college of Pathologists of Australasia Quality Assurance Program. Semin Thromb Hemost 32: 505-513, 2006.
4. Akin M, Karapinar YD, Balkan C, et al. An Evaluation of the DDAVP Infusion Test With PFA-100 and vWF Activity Assays to Distinguish vWD Types in Children. Clin Appl Thromb Hemost 2010; May 11. (Epub ahead of print)
5. Asatiani E, Kessler MC. Multiple congenital coagulopathies co-expressed with Von Willebrand's disease: the experience of Hemophilia Region III Treatment Centers over 25 years and review of the literature. Haemophilia 13: 685-696, 2007.

INTRODUCTION

Von Willebrand disease (VWD) and haemophilia A are the two most common inherited bleeding disorders. Worldwide incidence of VWD is estimated as between 1% and 4% without apparent racial or ethnic predilection.[1] In the United States, the incidence of haemophilia A is estimated to be 25 per 100.000 male births. VWD is classified into three major categories: partial quantitative deficiency (type 1), qualitative deficiency (type 2) and total deficiency (type 3). Type 1 VWD affects approximately 75% of symptomatic persons who have VWD.[2] A diagnosis of type 1 VWD is harder to establish when the VWF level is not markedly low but instead is near the lower end of the normal range. The most common symptoms associated with VWD are epistaxis, bleeding after minor surgical procedures, bruising and menorrhagia. The bleeding tendency, however, is highly variable and depends on the type and severity of the disease. In many patients with type 1 VWD, the bleeding tendency may be mild or absent.[3] Descriptions of congenital coagulopathies co-expressing with VWD are uncommon in the medical literature.

We describe a 1-year-old male with confirmed mild haemophilia A co-existing with mild type 1 VWD.

CASE REPORT

A 1- year -old male was admitted to our hospital with a history of excessive bleeding following circumcision. Initial laboratory evaluation revealed a prolonged activated partial thromboplastin time (APTT) of 46.2 s (normal range 23.2-34.7) , and low FVIII activity level of 5.5% of normal. Serial measures of FVIII activity ranged between 5% and 6%. A diagnosis of mild haemophilia A was made.

His mother was thought to be a carrier of haemophilia A as she had a prolonged APTT, and a low FVIII activity of 25%. She was also carrier for FVIII C2 domain R2304H gene mutation. Although there was no known family history of hereditary bleeding disorders, his father reported epistaxis, prolonged bleeding after shaving and circumcision. His father had a normal APTT, but a low FVIII activity of 43%, slightly low VWF:Ag level of 61%, and slightly low VWF:RCo activity of 62%. His father had a diagnosis of mild type 1 VWD.

Her subsequent evaluation, was also consistent with mild type 1 VWD with a decreased VWF antigen (VWF:Ag) of 50%, decreased ristocetin cofactor activity (VWF:RCo) of 44%. The DNA testing detected a C2 domain R2304H mutation of the FVIII gene. The child subsequently was diagnosed with mild haemophilia A co-existing with mild VWD type 1.

Tests were repeated twice and revealed the same results. Our patient had blood group A . It has been reported that blood type O is associated with VWF levels approximately 25% lower than non-O blood type. However in our previous study, no difference was found between O blood type and non-0 blood type in terms of VWF:Ag levels.[4] Multimeric analysis of plasma VWF, VWF: FVIII binding assay and mutation analysis for haemophilia A were done in Antwerp University and the results are reported in Table 1.

Laboratory tests of both parents were repeated and the results did not change. The blood sample was stored at -80^{0}C for a maximum period of 2 weeks to detect VWF:RCo, VWF:Ag, FVIII:C levels. Test results are reported as a percentage (%) of mean normal. VWF:RCo levels (normal ranges: 60-160%) were detected by aggregometry (Bio / Data Corporation, Horsham, PA, USA). VWF:Ag levels (normal ranges: 60-150%) were determined using a latex immunoassay using the STA- Compact analyzer (Diagnostica Stago, Asniéres, France). Factor VIII coagulant (FVIII:C) activity (normal ranges: 50-150%) was assayed by means of automatic coagulation machines (Sysmex, CA- 1500, Japan) using FVIII deficient plasma. Platelet function analyses were done in the patient, his father and mother. All responses to agonists -ADP, Collagen, epinephrine and ristocetin- were in the normal ranges in all family members.

DISCUSSION

Von Willebrand disease and haemophilia A are the most common inherited bleeding disorders. Despite the relatively high frequency of those two bleeding disorders in the general population, the reports of their coexistence together or of combined coagulopathies in general are rare. We describe a 1-year-old male with confirmed mild haemophilia A

6. Casonato A, Pontara E, Sartorello F, et al. Combined hemophilia A and type 2 von Willebrand_s disease: defect of both factor VIII level and factor VIII binding capacity of von Willebrand factor. Haematologica 86: 1110-1111, 2001.
7. Casonato A, Pontara E, Boscaro M, et al. Combined haemophilia A and type I von Willebrand_s disease: a family study including an evaluation of the effects of DDAVP infusion. Haematologica 25: 57-67, 1993.
8. Miller CH, Hilgartner MW, Harris MB, et al. Concurrence of von Willebrand's disease and hemophilia A: Implications for carrier detection and prevalence. Am J Med Genet 24: 83-94, 1986.
9. Casonato A, Pontara E, Sartorello F, et al. Combined hemophilia A and type 2 von Willebrand's disease: Defect of both factor VIII level and factor VIII binding capacity of von Willebrand factor. Haematologica 86: 1110-1111, 2001.
10. Nitu-Whalley IC, Hermans C, Lee CA. Prevalence of clotting factor deficiencies in a large population with von Willebrand disease. Thromb Haemost 84: 514-515, 2000.

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