

# Co-existing mild Hemophilia 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. The worldwide incidence of VWD is estimated between 1% and 4% of the population without apparent racial or ethnic predilection.

In the United States, the incidence of haemophilia A is estimated to be 25 per 100 000 male births. 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 1- year old male who was admitted to our hospital with a excessive bleeding after circumcision. Results: Laboratory evaluation revealed a prolonged activated partial thromboplastin time 46.2 sn (normal range 23.2-34.7) and low FVIII activity level of 5.5% of normal, von willebrand factor antigen and von willebrand factor ristocetin cofactor activity were also low at %50 and %44 of normal, respectively. Factor VIII C2 domain R2304H mutation was found. Conclusions: The propositus was now diagnosed with mild type 1 VWD in addition to mild severity haemophilia A. We believe that the co-existence of VWD and haemophilia A is underappreciated, under-diagnosed, and under-reported, given the fact that these are the two most commonly inherited coagulopathies.

**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 alıtsal kanama bozukluğudur. Dünyadaki vWH sıklığının etnik veya ırksal bir ayırım yapmaksızın %1-4 arasında olduğu tahmin edilmektedir. Amerika Birleşik Devletlerinde HA görülme sıklığı ise 100.000 erkek doğumda 25 olarak bildirilmektedir. Genel popülasyonda bu iki kanama bozukluğunun nisbeten sık görülmelerine rağmen birbirleriyle birlikte seyretmeleri nadir olarak rapor edilmektedir. Sünnet sonrası aşırı kanama ile kliniğimize başvuran 1 yaşında bir erkek hastada bu birlikteliği tanımladık. laboratuvar bulgusu olarak aPTZ: 46.2 saniye (N: 23.2-34.7) ve FVIII: %5 bulunması yanısıra düşük oranda vWF antijeni (%50) ve Ricof aktivitesi (%44) saptandı. Anne ve çocukta FVIII mutasyonu çalışılarak C2 bölgesinde R2304H saptandı. Olguya hemofili A ve hafif tip von Willebrand hastalığı (Tip 1) tanısı konuldu. Bu iki hastalığın en yaygın kalıtsal koagulopatiler olduğu göz önüne alındığında daha az bilindiği ve daha az teşhis edildiği ve rapor edildiğine inanıyoruz.

**Anahtar Kelimeler:** Hemofili, von Willebrand hastalığı

## INTRODUCTION

Von Willebrand disease and haemophilia A are the two most common inherited bleeding disorders. The worldwide incidence of VWD is estimated between 1% and 4% of the population without apparent racial or ethnic predilection.<sup>1</sup>

In the United States, the incidence of haemophilia A is estimated to be 25 per 100 000 male births. Von Willebrand disease has been classified into three major subtypes based on the qualitative or quantitative properties of VWF protein. Type 1 VWD is essentially a quantitative synthetic deficiency state of all VWF multimer sizes.<sup>2</sup> Inherited predominantly in an autosomal manner, VWD is now appreciated to be the most common heritable coagulopathy. The clinical presentation of VWD is variable. Haemorrhagic complications in affected individuals typically resemble platelet-type bleeding, i.e. easy bruising, mucocutaneous bleeding, menorrhagia, postpartum bleeding, and haemorrhage with minor surgical procedures.<sup>3</sup> 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 family in which hemophilia A and VWD were simultaneously present: A boy with both mild hemophilia A and mild type 1 VWD whose mother is a carrier of Hemophilia A and father with a diagnosis of mild type 1 VWD.

## CASE REPORT

1- year old male was admitted to our hospital with a excessive bleeding after circumcision. Laboratory evaluation revealed a prolonged APTT 46.2 sn (normal range 23.2-34.7) and low FVIII activity level of 5.5% of normal, vWF:Ag and VWF:Rco were also low at %50 and %44 of normal, respectively. Serial measures of FVIII activity ranged between 5% and 6 %. Tests were repeated two times and revealed same results. Patients' blood type is A. Blood Type O is associated with vWF levels approximately 25% lower than non-O blood type. In our study, no difference was found between O blood type and non-O blood type in terms of VWF: Ag levels.<sup>4</sup>

His father and paternal grandfather had a history of epistaxis, prolonged bleeding after shaving and ex-

cessive bleeding after circumcision. The laboratory findings of proband's father showed normal aPTT, FVIII: 43%, vWF:Ag: 61% and vWF:RCo: 62% and his mother's laboratory results revealed normal aPTT, FVIII: 25%, vWF:Ag: 77%, vWF:RCo: 79%. The laboratory tests were also done two times for mother and father and results did not show and difference. Blood sample was stored at -80°C for a maximum period of 2 weeks to detect VWF:RCo, VWF:Ag, FVIII:C levels. Test results was 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, Asnières, 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 child, father and mother. All responses to agonists -ADP, Collagen, epinephrine and ristocetin- were in the normal ranges in all family members .

It was thought that the mother is a carrier of Hemophilia A or had VWD type 2N and father had a diagnosis of VWD type 1. VWF multimer analyses, VWF: FVIII binding assay and mutation analyses for Hemophilia A were done in Antwerp University and the results are reported in Table 1.

We would conclude that his father shows no evidence for VWD in these samples but may have a slight VWD type 1, his mother is a carrier of Hemophilia A with no evidence for VWD. The propositus was now diagnosed with mild type 1 VWD in addition to mild severity haemophilia A.

## DISCUSSION

VWD and hemophilia A are the most common inherited bleeding disorders.; therefore, coagulation defects co-existing with VWD should occur commonly enough to merit increased awareness. The likelihood of co-existing coagulopathies should increase in populations where inter-related marriages are common.

Combined inherited coagulopathies coexisting with VWD are not uncommon and frequently are phe-

<b>Table1.</b> Von Willebrand disease and Hemophilia-A laboratory data				
	<b>Normal range</b>	<b>Father</b>	<b>Mother</b>	<b>Child</b>
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

notypically divergent from classical VWD.<sup>5</sup> Haemophilia A is the most common congenital coagulopathy to co-exist with VWD. Additional hereditary coagulopathies coexisting with VWD were suspected when coagulation laboratory results atypical for VWD were observed; when family history of bleeding complications did not match the characteristic clinical pattern for VWD; and when the severity and character of bleeding manifestations were out of proportion to those signs and symptoms expected with isolated VWD. Casonato et al. reported one case of haemophilia A associated with VWD type 2N<sup>6</sup> and another case in which mild VWD type 1 co-existed with severe haemophilia A.<sup>7</sup> Another clinical report<sup>8</sup> described five families with co-existing haemophilia A and VWD. The authors admitted that the presence of VWD confounded their ability to confirm the carrier status of obligate family members for haemophilia A.

We describe individual with confirmed mild haemophilia A co-existing with mild type 1 VWD. In Turkey, aPTT is rarely checked before circumcision and mild prolongation of aPTT are generally thought to be a result of technical problem. In Turkey approximately 100% of boys underwent circumcision. Bleeding following circumcision becomes an important clue for the patients with mild hemophilia especially the boys who is the first son of the family. In comparison, two mutations that we observed to be stable but deficient only in vWF bin-

ding function (P2300S and R2304H) are associated with variable and mild disease, respectively.<sup>9</sup>

Replacement therapy for acute haemorrhage was aimed at their haemophilia A and no special adjustments were made for their VWF activities although the preferred FVIII replacement product for their care contains significant amounts of VWF (Haemate-P). 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). We believe that the co-existence of VWD and haemophilia A is underappreciated, under-diagnosed, and under-reported, given the fact that these are the two most commonly inherited coagulopathies

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