

## Original Research Article

# Investigation of Von Willebrand disease in children with epistaxis and clinical practical approach

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### ABSTRACT

**Background:** The absence of a standardized approach to the disease and bleeding history can lead to unnecessary patient consultations and sometimes late diagnosis. The aim of this study was to investigate von Willebrand disease (VWD) in patients presenting with epistaxis with clinical practical approach.

**Methods:** 63 Patients who were admitted to the pediatric hematology and oncology clinic between June 2017 and June 2018 with a complaint of epistaxis were evaluated. Patients diagnosed with VWD were classified as group 1, patients without VWD considered as group 2. The two groups were compared in terms of number of additional symptoms, and family history.

**Results:** There was no difference in terms of age and gender when compared with 42 patients not considered as VWD (group 2), number of additional symptoms, and family history were significantly higher in the group considered as VWD.

**Conclusions:** Excess number of additional bleeding symptoms, and bleeding history in family are of importance for the suspicion of diagnosis of VWD for physicians with limited experience in terms of bleeding disorders in primary and secondary health care institutions.

**Keywords:** Bleeding, Bleeding disorders, Bleeding symptoms, Epistaxis, Mucocutaneous menorrhagia, Von willebrand disease

### INTRODUCTION

Von Willebrand disease (VWD) is the most common bleeding disorder in the community. VWD is caused by deficiency or dysfunction of the Von Willebrand factor (VWF), which mediates adhesion of platelets in vascular injury sites and also binds to factor VIII, stabilizes and thus prolongs half-life in circulation.<sup>1</sup> The question of detailed bleeding history and family history and the abnormal VWF laboratory results play a key role in the diagnosis. The diagnosis of severe and moderate type of disease is usually made in childhood, and diagnosis may be delayed until adulthood in patients with mild type VWF deficiency.<sup>2</sup>

Epistaxis is one of the most common causes of consultation to pediatric hematology in childhood. Despite being frequent, there is often no underlying bleeding diathesis.<sup>3</sup> The absence of a standardized approach to the disease and bleeding history can lead to unnecessary patient consultations and sometimes late diagnosis. Therefore, bleeding scoring systems have been developed.<sup>4</sup> The aim of this study was to investigate von Willebrand disease in patients presenting with epistaxis with clinical practical approach.

## METHODS

63 patients who were admitted to the pediatric hematology and oncology clinic between June 2017 and June 2018 with a complaint of epistaxis were evaluated. Questions were answered by parents of children under the age of 12, and the questions were answered by children over 12 years of age or who showed the required developmental capacity. Age, gender, bleeding symptoms, family history, Von Willebrand Factor Antigen (VWF: Ag), Ristocetin Cofactor (VWF: RCo) and factor VIII levels of the patients were evaluated. VWD was diagnosed through the evaluation of VWF: Ag, VWF: RCo and factor VIII levels. Patients with VWF: RCo / VWF: Ag ratio less than 0.5 were not detected. Since Type II VWD was not considered, no patient multimer analysis was requested. Patients diagnosed with VWD were classified as group 1, patients without VWD considered as group 2. The two groups were compared in terms of age, gender, additional number of symptoms, and family history. The study was evaluated and approved by the local ethics committee.

### Statistical analysis

The normality of distribution of continuous variables was tested by Shapiro Wilk test. Mann Whitney u test was used to compare 2 independent group for non-normal data. Kruskal Wallis and Dunn multiple comparison tests were used to compare non-normal data across three groups. Chi-square test applied to investigate relationship between 2 categorical variables. Statistical analysis was performed with SPSS for Windows version 24.0 and a P value <0.05 was accepted as statistically significant.

## RESULTS

The results of, VWF: RCo and factor VIII were evaluated and VWD was diagnosed in 21 patients (group 1). Group 1 consisted of 8 males and 13 females. 9 of females were in menstrual period and VWF: Ag 8 had menorrhagia. There was no difference in terms of age and gender when compared with 42 patients not considered as VWD (group 2), but number of additional symptoms, and family history were significantly higher in the group considered as VWD (Table 1).

Epistaxis was the only symptom in one patient in the VWD group and 15 in the other group. When the frequency of symptoms was evaluated, the most common symptoms except epistaxis were mucocutaneous bleeding and menorrhagia. The rarest ones were gastrointestinal hemorrhage and hemarthrosis. The patients had no history about central nervous system hemorrhage.

There was a significant difference between the two groups in terms of cutaneous bleeding, bleeding during tooth extraction, gingival hemorrhage, more bleeding than expected in circumcision and after operation, and hemarthrosis (Table 2).

**Table 1: Comparison of two groups in terms of gender, bleeding scores, number of symptoms, and family history.**

	Von Willebrand Disease (n=21)	Control group (n=42)	P
Gender‡			
Male	8(38.1)	10(23.8)	0.237
Female	13(61.9)	32 (76.2)	
Family history‡	16 (76 )	6 (14 )	0.001 *
Age†	13 [6-14]	11 [6-13]	0.371
Number of symptoms‡	3[2-3]	2[1-2]	0.001 *

\*Significant at 0.05 level

† Median[25%-75%]; Mann Whitney u test

‡ n(%); Chi-square test.

**Table 2: Comparison of two groups in terms of the frequency of symptoms.**

Symptoms (n(%))	VWD (n=21)	Controls (n=42 )	P
Epistaxis	21 (100 )	42 (100 )	1.000
Menorrhagia	7 (53 )	16 (50 )	0.815
Ecchymosis	12 (57 )	8 (19 )	0.002*
Bleeding after tooth extraction, mucous membrane bleeding	7 (33 )	3 (7 )	0.007*
Bleeding after circumcision	2 (1 )	0 (0 )	0.042*
GIS hemorrhage	1 (5 )	1 (2 )	0.611
Hemarthroses	3 (14 )	0 (0 )	0.012*

\*Significant at 0.05 level; Chi-square test

## DISCUSSION

Epistaxis is common in healthy children and is seen in 40%. However, epistaxis is also an important finding of von Willebrand Disease. In a study conducted by Sanders et al in 113 children with VWD, the first complaint of 26 patients was epistaxis. The incidence of epistaxis was detected as 56% in this study.<sup>5,6</sup> The incidence of epistaxis in adults is lower. This ratio was found to be 25% in the study conducted by Mauer et al in 500 healthy adults.<sup>7</sup> Decrease in activity by child age group and increase in VWF: Ag by age may be the cause of complaints in adults is rarely seen.

VWD is the most common bleeding disorder as estimated in 2 large studies, one by in school children and the other a multithnic study. However, in two studies, all children with or without bleeding symptoms were examined and it is thought that this ratio is higher in children with bleeding symptom.<sup>8,9</sup> To provide proper screening for VWD in children with epistaxis and to identify patients who will be referred to advanced examinations, it reveals

the question of whether the disease history alone is reliable or not. For this reason, different bleeding scoring systems have been used in adults for VWD diagnosis and then adapted to children. Quantitation of mucocutaneous bleeding symptoms in children with VWD is possible using the pediatric bleeding questionnaire, a pediatric adaptation of a standardized adult bleeding questionnaire.<sup>4,10</sup> In a study of Mittal et al. conducted on 1281 healthy and 35 VWD children, they found a sensitivity of 97.2% and a specificity of 97.1% for the diagnosis of VWD in patients who score 3 or more on the bleeding score.<sup>11</sup> But also in our country where the number of sick children is too much, using bleeding questionnaire is not always practical in outpatient clinic.

The frequency of epistaxis in children varies according to age groups. Epistaxis is seen more frequently during play and schoolchildren because of the frequent occurrence of upper respiratory tract infections and local traumas. When bleeding diathesis occurs, the onset of symptoms may be seen earlier or age distribution may change depending on the underlying disease.<sup>12,13</sup> In my study epistaxis was not classified according to age because it can be seen at every age in childhood group and also because of the low number of the patients.

In a multicenter study in which Type I Von Willebrand patients were evaluated, the median bleeding score was the same (7.0) in both males and females. Meanwhile, the mean age of males was found to be 9.5, while the mean age of females was 12.5. Hemorrhage symptoms were higher in males due to higher physical activity during early childhood and bleeding scores increased in females due to menorrhagia during adolescence.<sup>14</sup> In my study, there was no significant difference in number of symptoms between females and males in the group who had VWD diagnosis. However, the presence of menorrhagia in adolescents suggests that questioning menorrhagia at first admission is particularly important in terms of diagnosis.

VWD is a genetically transmitted disease. Type 3 and Type 2N VWD show inheritance as autosomal recessive (OR) while Type 1, Type 2A, Type 2B, Type 2M show inheritance as autosomal dominant (OD). Male and female are equally affected in VWD with autosomal inheritance. In the case of OD inheritance, each child born from sick mother (father) and healthy father (mother) is likely to be 50% sick. In OR inheritance, the probability of being sick is 25%, the probability of being healthy is 25%, the probability of being a carrier is 50%. The presence of a documented bleeding disorder in a family member is extremely useful when deciding which individuals need to be assessed more.<sup>15,16</sup> Especially questioning the family history is important during the diagnosis phase. In my study, 16 of 21 patients in group 1 had a family history of bleeding. Compared with Group 2, the rate was found to be significantly higher.

The greatest limiting factor in my study was the low number of patients due to be a single centered study. I think that a multicenter, more patient-based study could give more precise information about the frequency and the incidence of VWD in patients with epistaxis and epistaxis etiology.

## CONCLUSION

In conclusion, the use of pediatric bleeding scoring systems in children with epistaxis can help clinicians differentiate between significant bleeding disorder and insignificant bleeding common among children. But also, for physicians with limited experience in terms of bleeding disorders apart from hematologic professionals, in outpatient clinic, excess number of additional bleeding symptoms, and bleeding history in family are of importance for the suspicion of diagnosis of VWD practically.

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