Von Willebrand's Disease in German Shepherd Dogs in The Marmara Region (Turkey)

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SUMMARY

Plasma von Willebrand factor antigen (vWf:Ag) concentrations were determined for 204 German Shepherd Dogs with the ELISA method using the Asserachrom test kit. Other hematological parameters, in particular platelet number, as well as additional parameters such as buccal mucosa bleeding time (BMBT) were evaluated. The plasma vWF antigen concentration was found to be significantly reduced in dogs affected with von Willebrand's disease (vWD) while BMBT had increased. Plasma vWf:Ag concentration in all dogs ranged from 0.1 % to 180 %.

In particular dogs trained for military purposes such as bomb and mine detection or as track hounds, carry out important tasks in the field on which the lives of soldiers depend. As a result of this study the disease was discovered in dogs which had been trained for such special tasks at a large expense of time and money. The study came to the conclusion that absence of this factor must be applied as a criterion of dogs selection for breeding by these organisations.

Keywords : German Shepherd Dog - von Willebrand disease - von Willebrand factor.

RÉSUMÉ

Maladie de von Willebrand constatée chez les Chiens de Berger allemands, dans la région de Marmara (Turquie). Par A. KAYAR, M.E. OR, R. GÖNÜL, E. AKDENIZLI, Ç. PARKAN, U. BAKIREL et H.T. DODURKA.

La concentration plasmatique en facteur de von Willebrand facteur antigène (vWF:Ag) a été étudiée sur 204 bergers allemands, par la méthode ELISA (test Asserachrome). D'autres paramètres tels le nombre de thrombocytes et le temps de saignement de la muqueuse buccale (BMBT) furent évalués. Une diminution de la concentration plasmatique en antigène de vWF et une augmentation du BMBT ont été notés chez les chiens atteints. La concentration en antigène de vWF variant de 0,1 à 180 % sur l'ensemble des animaux de l'étude. Ces résultats suggèrent que ce critère doit être pris en compte lors de la sélection des chiens utilisés par l'armée, aussi bien en ce qui concerne l'achat d'animaux que lors du choix des reproducteurs.

Mots-clés : Berger allemand - maladie de von Willebrand - Facteur von Willebrand - saignement - coagulation - hemostase - maladie génétique.

Introduction

Von Willebrand's disease (vWD) is the most common inherited bleeding disorder in dogs, identified in about 54 breeds, as well as in humans. It is caused by a deficiency or abnormality of von Willebrand factor [2, 5, 10, 15, 21]. The condition is found in particular in German Shepherd dogs but in other dog breeds such as Doberman Pinscher, Scottish Terrier, Golden Retriever, Basset Hound, Standard Poodle, Shetland Sheepdog, Rottweiler, Standard Manchester Toy Terrier and Daschund [12, 20, 27, 29, 30, 31, 37]. The wWF is a large glycoprotein that circulates in the blood as a complex with factor VIII, and is necessary for a number of very important biological functions such as factor VIII stabilization and adhesion of platelets to the subendothelium [6, 9, 10, 15, 17, 21].

vWD is characterised by high morbidity and low mortality [12, 23]. The spectrum of clinical findings in dogs affected with von Willebrand's disease ranges from none to severe hemorrhagic diathesis resulting in death [2, 21]. As a clinical condition, bleeding may occur only in the postoperative period, while in other cases the animals affected with vWD suffer from spontaneous repeat bleedings [2, 10, 15]. Other clinical conditions characterising the disease are repeated hematuria, serosanguineous otitis externa, excessive bleeding after extraction of teeth or gum injury, vagina and penis bleeding, epistaxis, lameness, melena, purpura, prolonged bleeding from vaccination, cut nails or wounds, increased cutaneous bleeding, especially after venipuncture [4, 12, 15, 33, 38]. The disease is characterised by prolonged bleeding time, while the number of platelets remain normal and activated partial thromboplastin time (APTT) and activated clotting time (ACT) are either normal or slightly increased. Also prothrombin time (PT) and thrombin time (TT) are unaffected [10, 24, 38].

It has been reported that in dogs hypothyroidism exacerbates the congenital von Willebrand disease and causes acquired von Willebrand's disease [11, 12].

With respect to the clinical severity of the disease, its hereditary property, and the quality, structure and function of the vWF proteins, vWD is classified into 3 major types [5, 17]. Type I, the most prevalent form, constitutes 90% of all cases. This form is characterised by a reduced amount of vWF:Ag. The clinical symptoms range from light to severe bleeding [33, 34]. Type II is identified by structurally abnormal vWF and severe clinical symptoms, and has been reported in German Shorthaired and Wirehaired Pointers [3, 19]. Type III is rarely observed; von Willebrand factor is completely absent from the plasma or present in only trace amounts and it is a severe form [8, 17, 23]. This type of disease has been identified in Schottish Terriers, Chesapeake Bay Retrievers and Dutch Kooikers [18, 25, 36].

Parry [22] reported that the disease can be diagnosed by measurement of vWF concentration or activity, and that a normal bleeding time did not exclude a diagnosis of vWD. In the case of normal bleeding time it was necessary to measure APTT and PT. Studies of non-carrier and carrier Kooiker Dogs did not reveal a significant difference in plasma vWF concentrations and required an additional DNA test. Work has been undertaken to develop this technique [36].

Brooks *et al.* [6] examined 467 German Wirehaired Pointer Dogs; they found 376 (81%) to be non-carriers, 28 (6 %) borderline cases, 58 (12 %) carriers and 5 (1 %) dogs affected with vWD. In their classification of the individual results, the researchers interpreted vWF antigen values of 70-179 % as non-carrier, 51-69 % as borderline, 2-46 % as carrier and 0.1-0.3 % as affected with vWD.

In another study on Shetland Sheepdogs [23] vWF antigen values exceeding 60 % were considered non-carrier, 50-59 % as borderline, and 0-49 % as carrier.

With the development of the ELISA technique for vWF in dogs new and more sensitive methods have been proposed [25, 26, 28, 35]. With the ELISA method, the cross reaction capability of plasma proteins with vWF protein-specific antibodies is measured [23]. Structural components of the vWF multimers are used for the differentiation of the various vWD types [13, 38].

In the field of veterinary medicine, no study has been carried out as yet on this disease in Turkey. In particular dogs trained for military purposes such as bomb and mine detection or as track hounds, carry out important tasks in the field on which the lives of soldiers depend. The purpose of this study was to measure the concentration of plasma vWF:Ag in dogs which had been trained for such special tasks at a large expense of time and money, with the aim of applying the absence of this factor as a criterion of elimination for those organisations when selecting dogs for breeding.

Material and Methods

In this study 204 German Shepherd Dogs, 42 female, 162 male, trained for police and military purposes, were examined. The dog keepers were asked to provide general information on the dogs such as age, sex, weight, character as well as about bleeding-related incidences. The records of the dogs were examined and lineages of relationship established. Similar to the technique applied by Brooks *et al.* [5], only the family tree of offsprings of carrier mothers and fathers were investigated. With a Medonic CA 570 haemographic instrument, a total blood count including red blood cells (RBC), packed cell volume (PCV), Hemoglobin (HGB), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelet (PLT) and white blood cell (WBC) were carried out.

For vWF:Ag determination, blood samples (9 parts) were taken from the vena jugularis and pipetted into test tubes containing 1 part sodium nitrate (3.8 %). The tubes were centrifuged for 10 min at 2,000 rpm and the plasma separated and stored at -70°C until the test. The vWF values were determined with the technique described by Arnold *et al.* [1] using a commercially available Asserachrom® vWF test kit (Diagnostica Stago) based on the ELISA method. In accordance with the criteria proposed by Brooks *et al.* [6], the dogs were classified on the basis of their vWF values as non-carrier, borderline, carrier and affected. In order to determine bleeding time, the buccal mucosa bleeding time (BMBT) was also performed as described by Stokol and Parry [32]. The hematological parameters of the dogs in each group and their BMBT results were evaluated statistically with the Duncan test [14].

Results

The age distribution of the 204 German Shepherd Dogs examined in this study was : 3-5 months 10.34 % ; 6-11 months 6.89 % ; 1 year 10.34 % ; 2 years 31.07 % ; 3 years 17.24 % ; 4 years 6.89 % ; 5 years 6.89 %, and 6 years and older 10.34 %. After interviews with the keepers of each individual dog, it was established that in 4 % of the dogs one-sided or two-sided epistaxis and blood clotting was delayed after castration or injuries. The animals (other 2 %, except affected 2 %) were in carriers group. Their BMBT's were around 5 minutes.

The results of the vWF:Ag concentration measurement and their classification showed that 51 % (n=104) of the dogs were non-carriers, 23 % (n=47) borderline cases, 24 % (n=49) carriers and 2 % (n=4) had developed the disease (Table I). The determining ranges for the vWF values were set as follows : 70-180 % non-carrier ; 50-69 % borderline ; 2-46 % carrier ; 0.1-0.3 % affected. It was found that all

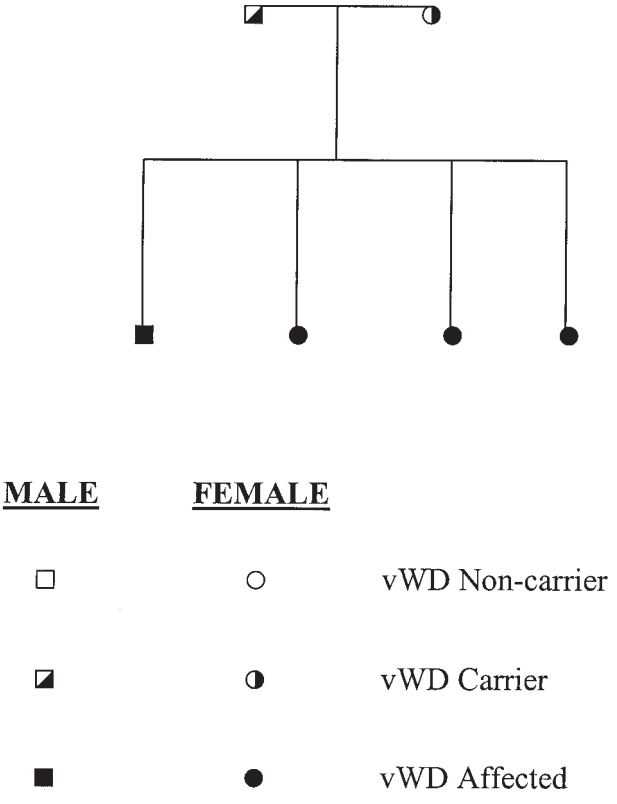

FIGURE 1. — Family tree of 4 German Shepherd Dogs affected by von Willebrand's disease (vWD).

	VWD Classification			
	Non-Carrier	**Borderline**	**Carrier**	**Affected**
Range of vWF:Ag (in %)	70-180	50-69	2-46	0.1-0.3
No of valid tests	104	47	49	4
%	51	23	24	2

TABLE I. — Plasma von Willebrand Factor (vWF) concentrations in 204 German Shepherd Dogs.

	Non-Carriers		**Borderline**		**Carriers**		**Affected**	
	(n=104)		**(n=47)**		**(n=49)**		**(n=4)**	
Parameter	**S**	**SX**	**S**	**SX**	**S**	**SX**	**S**	**SX**
RBC ($x10^6/mm^3$)	7.5±1.3[a]		6.2±3.5[a]		5.6±4.7[a]		3.8±1.9[b]	
PCV (%)	40±2.1[a]		42±3.7[a]		36±2.7[a]		23±5.2[b]	
HGB (g/dL)	12.9±0.7[a]		14.1±1.3[a]		11.8±2.4[a]		7.8±1.3[b]	
MCV (fl)	72±2.5[a]		65±0.8[a]		73±2.1[a]		78±1.2[a]	
MCH (pg)	21±1.4[a]		24±3.4[a]		28±8.6[a]		25±1.7[a]	
PLT ($x10^3/\mu L$)	500±27.3[a]		400±33.2[a]		600±42.3[a]		500±10.5[a]	
WBC ($x10^3/mm^3$)	9±2.6[a]		8.5±1.8[a]		10.4±2.7[a]		10.2±2.1[a]	
BMBT (min)	2.62±0.65[a]		4.77±1.01[b]		4.17±0.81[b]		14±2.8[c]	

a,b,c : A significant difference of $p<0.01$ was found between values with a different letter in each of the columns.

TABLE II. — Mean values and standard deviations of hematological parameters and buccal mucosa bleeding time (BMBT) in groups of 204 German Shepherd Dogs as a function of vWF concentration.

diseased dogs (1 male and 3 females) were siblings with their parents being carriers (Figure 1). These diseased dogs were 2 years old.

The hematological parameters of each group as well as the mean values of the BMBTs including standard deviations are given in Table II. It was found that the mean values for RBC, PCV and HGB of the dogs affected with vWD were lower than the mean values of the dogs in all other groups. This difference was determined to have a statistical significance of $p<0.01$. Examination of the hematological parameters of each group revealed anemia (normocytic-normochromic) in the group of the dogs affected with vWD. It was also found that the BMBT value was higher in the groups of borderline cases and carriers with respect to the non-carrier dogs, while the highest overall values were found for the group of sick animals, with a statistically important significance for those differences of $p<0.01$. The platelet number was found to be within normal limits of 400-600 µ/l, with no statistically significant difference between the various groups.

Discussion

Despite the fact that vWD is one of the important and wide-spread hereditary coagulopathies, it is difficult to identify and to diagnose [12, 27, 29]. It has been reported that some forms of the disease, which are prevalent in dogs, are so mild that they are of questionable clinical significance [17]. Castaman *et al.* [8] point out that with a prevalence of 1 % in the general population, the ratio of visible clinical symptoms is only 0.01 %.

Brooks *et al.* [6] examined 467 dogs of which they found 81 % to be non-carriers, 6 % borderline cases, 12 % carriers and 1% to have developed the disease. In view of those results, the ratios of prevalence found in this study are in line with other reported values [5, 26, 35]. In line with the findings of Brooks *et al.* [6], it was also established in this investigation that the offsprings of carrier fathers and mothers had developed the disease. Those results emphasise the importance of the risk associated with spreading this hereditary disease.

In a study on three dog breeds, Brooks *et al.* [7] found the concentration of vWF:Ag in Doberman pinshers to be 15 % on average, in Shetland Sheepdogs 8 % and in Scottish Terriers 0 %. Slappendel *et al.* [25] screened 717 Dutch Kooiker Dogs and in 38 of them identified Type III vWD. The wWF:Ag contentration in those dogs was found be less than 1.6 %. In the present study the ratio in dogs affected with vWD was 0.1-0.3 %. Brooks *et al.* [7] determined the average age of disease development in a study on Doberman Pinschers, Scottish Terriers and Shetland Sheepdogs as 4.6 years, 1.7 years and 1.9 years respectively. This led us to the conclusion that no correlation exists between the occurrence of the disease and the animal`s age.

The disease is characterised by high morbidity and low mortality with usually normal platelet number [5, 17, 21]. In this study no difference could be established between the groups of non-carriers, borderline cases, carriers and affected dogs with respect to their platelet numbers. Confirming the findings of other researchers [6, 15], a statistically significant reduction in the RBC, PCV and HGB parameters, which were used for anemia evaluation, was found in the

group of diseased animals as compared to the other groups. Similarly, also the clinical symptoms revealed the occurrence of anemia in the dogs affected with vWD. As has been reported by a number of researchers [16, 18, 24, 26, 28] a statistically significant increase of BMBT was found for the group of animals affected with vWD also in the present study. We are of the opinion that those changes are related to the development of an abnormal thrombocyte function. The results are further substantiated by the information of the keepers of the diseased dogs who complained of bleeding problems.

Clinical signs identified in this study such as delayed blood clotting after one-sided or two-sided epistaxis, castration or injuries sustained by the diseased dogs, and laboratory findings such as low values of vWF and anemia could also be observed in the parents of the affected dogs.

In one study the BMBT value for 38 Dutch Kooiker Dogs afflicted by Type III vWD was found to be higher than 10 min [25]. In the present study 14 min were measured for the diseased dogs which conforms to those reported values. It is assumed that the extension of the bleeding time in those dogs is connected to a deficiency` in vWF and coagulation disorder.

Stokol *et al.* [31] recommended that steps be taken to reduce the prevalence of the disease and thereby the number of clinically affected dogs, such as the establishment of a national testing scheme to determine the vWD status of all breeding dogs. Dodds [12] suggested that affected dogs and carriers should not be bred or should be tested for von Willebrand's factor before breeding. In a study on Dutch Kooiker Dogs, which have a high prevalence of Type III vWD, it was recommended that dogs affected with vWD and nonsymptomatic carriers must be excluded to eradicate vWD from the breed [36].

For various reasons such as the country`s geopolitical position, internal events with an impact on internal security and stability, and natural disasters, the use of dogs for policing, military and rescue purposes has increased in Turkey over the last years. The proper training of those dogs is a lengthy and rather costly process. In particular dogs trained for military purposes such as bomb and mine detection or as track hounds, carry out important tasks in the field on which the lives of soldiers depend. As a result of this study, the disease was discovered in dogs which had been trained for such special tasks at a considerable expense of time and money. The study came to the conclusion that absence of this factor must be applied as a criterion of elimination by those institutions and organisations when selecting dogs for breeding. We are of the opinion that such institutions and organisations should routinely test their dogs for this disease, and absolutely avoid using affected or carrier dogs for breeding. It would also be advisable to carry out similar studies on the other dog breeds common in Turkey.

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