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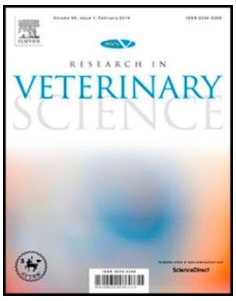

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Hemophilia A in a Belgian Shepherd Malinois dog: Case report

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Abstract

This case report presents a Belgian Shepherd Malinois dog affected by Hemophilia A recognized at the age of seven months. The clinical follow-up including all the diagnostic procedures leading to the final diagnosis and the course of this disorder are presented.

This is a typical proband case demonstrating the appearance of this genetic disease in a breed never involved by this coagulation disorder so far documented that started an intensive and laborious plan to reduce the incidence of Hemophilia A and the further appearance of new cases.

Keywords: Hemophilia A, Dog, Belgian Shepherd Malinois, Diagnosis, Treatment, Outcome

1. Introduction

Hemophilia A is the most common and usually severe inherited canine coagulopathy. Diagnosis is based upon documenting a combination of prolonged aPTT (activated Partial Thromboplastin Time) and a selective reduction in factor VIII (FVIII) activity and/or concentration. Hemophilia A is an inherited X-linked recessive disorder recognized in several breeds of dogs, predominantly affecting

males with females as carriers. Females may be homozygous (normal), heterozygous (carriers) or rarely, homozygous (recessive). New mutations can occur in which the defect appears in families without a history of the disease (Brooks, 2010, Barr and McMichael, 2012, Mischke, 2012).

The clinical severity of hemophilia A is generally dependent on both the magnitude of the deficiency of FVIII and the exposure to trauma. Animals affected can be classified as mild (FVIII 5-25%): with a low bleeding tendency; moderate (FVIII 2-5%): may suffer hemorrhagic problem to minor trauma; severe (FVIII< 2%): tend to have spontaneous hemorrhagic episodes (Brooks, 2010, Barr and McMichael, 2012, Mischke, 2012).

In this report, a case of Hemophilia A is demonstrated in a breed of dog never reported affected (Lubas et al., 2011). Further investigation confirmed other littermates with a reduction of FVIII activity (Lubas et al., 2012).

A young dog, male (nickname: GML), Belgian Shepherd Malinois (BSM), born May 5th, 2010 (8 months old), was referred to our Veterinary Teaching Hospital with a two months history of carpal swelling and occasional mild signs of bleeding from the mouth during deciduous teeth loss. The referring practitioner performed a laboratory work-up including complete blood count (CBC), coagulation profile and a two-view radiology of the carpus. The only remarkable and significant data obtained was a slight prolongation of the activated Partial Thromboplastin Time (aPTT = 15.2 sec, reference interval {RI};8.6-12.8). In addition, several coagulation factors (II, V, VII, VIII, IX, X, XI, and XII) were investigated, FVIII was clearly decreased (13%, RI 50-135) and FIX was mild reduced (53% RI 55-110). A tentative diagnosis of Hemophilia A was postulated at the age of 7 months.

During the referral exam, the owner who was a small stock breeder, reported that GML was co-inhabiting with three other adult dogs of the same breed. About 15 days before the referral visit, GML was involved in a fight with one of the dogs. He suffered a slow healing bite wound injury on the left shoulder with sero-hemorrhagic effusion in the subcutaneous space. The wound was treated locally

with antiseptic solution and a combination of amoxicillin-clavulanate (about 12 mg/kg bid) per os. The physical exam was otherwise unremarkable with a healthy growing dog weighing 24 kgs at 8 months of age. The only notable finding was a large swelling on the left shoulder, which upon palpation felt hard, cold and painless appearing to be formed by two bumps of about 4 cm in diameter. Diagnostics including CBC, serum biochemical profile, urinalysis, coagulation profile as well as the quantification of FVIII and vWF (von Willebrand factor) was carried out. The biochemical results showed only a slight increase in C-Reactive protein (0.70 mg/dl, RI 0-0.30), which was most probably due to chronic inflammation. The coagulation profile showed a slight increase of aPTT (19.8 sec, RI 9-18). A new FVIII activity testing performed at a different laboratory from the previous one, showed a clear reduction (6%, RI 70-135), while the vWF assay was within the normal range (108%, RI 55-150). A final diagnosis of hemophilia A was concluded.

The referring veterinarian did a precautionary follow-up to check for the appearance of any new bumps or other abnormalities including bleeding. GML followed a regular vaccination and endo-ectoparasite prevention protocol. Until the age of 12 months, GML was very active until he showed right rear leg lameness with a swelling due to a hematoma in the inguinal region causing compression of the femoral nerve (Fig. 1). An ultrasonography revealed a large capsulated hematoma in the muscle namely a myo-hematoma. GML was initially treated conservatively with a pain reliever, tramadol HCl 3 mg/kg bid per os with a later addition of tranexamic acid at 15 mg/kg bid per os. Two weeks later, GML presented a swelling in the tibio-tarsal joint (Fig. 2) with the enlargement of quadriceps muscles extending progressively to the entire leg. Further laboratory tests were performed which documented signs of inflammation including neutrophilia (10.5 x 10^9/L, RI 3.0-8.8), hyperfibrinogenemia (869 mg/dL, RI 150-550), elevated C-reactive protein 2.54 mg/dL, and prolonged aPTT 14.6 sec, (RI 8.6-12.8). Ultrasonography revealed a diffuse imbibition of muscles and surrounding tissue of the joint involved. GML was administered with 3 fresh frozen plasma (FFP) bags of about 150 ml each as an emergency

and initial treatment. During the last infusion of FFP, GML had a diffuse urticarial reaction and so the transfusion was discontinued and large dose of dexamethasone was given intravenously (1 mg/kg). Lameness and the hematomas resolved slowly in a period of about three weeks while on a conservative therapy per os with amoxicillin-clavulanate (12 mg/kg bid), low dosage of prednisone (0.8 mg/kg sid) which was slowly tapered down over 3 weeks and desmopressin (0.3 mcg/kg bid).

At the age of 17 months, there was a slight change in GML's behavior. He was more aggressive towards the dogs he was co-inhabiting with and lacked prompt recognition of the owner and her commands. During the following months, GML presented hematomas in the neck, trunk and rear part of the mouth. These episodes were treated with the same treatment as before including desmopressin, broad-spectrum antibiotics, and tranexamic acid. In one of these recurrent episodes, another FFP transfusion (two bags of 125 ml each) was administered. Before administering the FFP transfusion, a sensitivity test was performed subcutaneously to prevent any allergic reaction. The result was negative. The episodes of aggressiveness worsened and the owner found difficult to manage GML because he was aggressive towards anybody approaching him including the familiar veterinarian providing care. At the age of 22 months (February 2nd, 2012) GML was euthanized due to his clinical situation. The body for autopsy was not available.

The discovery of the proband for Hemophilia A in the BSM breed was a surprise for the breeders involved. Initially, most breeders deliberately ignored the occurrence of this genetic disease. A screening using the assay concentration of FVIII confirmed a genetic involvement of few families. Thanks to few cooperative breeders, a web site where all the information regarding this disease in BSMs is available nowadays (www.malinemo.net). Further investigation conducted in the littermates of GML disclosed that among 12 puppies delivered including the proband, there were 6 males and 6 females. Unfortunately, only three dogs were tested for the amount of FVIII activity (at the same laboratory). Two males (RSL and NOS, nicknames) resulted both with FVIII of 13% and one female

(QUN, nickname) resulted with FVIII of 39%. These data suggested mild disease in the males and the carrier status in the female. In addition, their mother was also a carrier (36% of FVIII). Unfortunately, we do not have any information regarding the clinical situation of GML's male siblings because breeders hesitate to disclose such information.

Regarding this single case of hemophilia A, there are two interesting findings:

GML's FVIII activity values were determined twice (at different laboratories) and found to be in the mild disease range (13% and 6%). No other bleeding disorders were recognized at the time to contribute to the signs and symptoms that appeared in this dog. There was only a slight reduction of FIX activity at the beginning but it was not investigated further due to the young age of the proband. After interviewing other practitioners and breeders, we found out that some other BSMs with approximately similar FVIII levels with those to GML's, some of which were half brothers, showed very mild signs of bleeding before the age of one year old. These mild signs were consistent with prolonged bleeding for minor trauma, which resolved favorably, but due to FVIII reduction, they have a normal span of life without any adverse effect. They also participated in full sport and utility activities, which is characteristic in this breed.

The treatment for the bleeding disorder was focused on the use of FFP for the acute case. In addition, a conservative therapy with NSAID and antibiotic cover was administered. More specifically, tranexamic acid and desmopressin were used resulting in a fair and apparent response in terms of reducing and halting the bleeding process. We however cannot argue about the efficacy of this collateral treatment as yet.

To breeders involved a consultation with the use of screening tests including a combination of aPPT and PT together with FVIII assay concentration was offered. This procedure will aid in limiting the disease.

Conflict of interest

The authors declare no conflicts of interest.

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159 Figure legend (picture in B/W)
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161 Fig. 1 Right rear leg lameness due to swelling caused by a hematoma in the inguinal region inducing a
162 compression of the femoral nerve in the BSM dog GML
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164 Fig. 2 Swelling in the tibio-tarsal joint in the BSM dog GML
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