

Hemophilia A in a Male Parson Russell Terrier Puppy

Aroch, I.,*¹ Tamarin, I.² and Kuzi, S.¹

¹ Hebrew University Veterinary Teaching Hospital and Koret School of Veterinary Medicine, Hebrew University of Jerusalem, P.O. Box 12, Rehovot, 761001, Israel.

² Laboratory of Hemostasis, Institute of Thrombosis and Hemostasis, and the National Hemophilia Center, Chaim Sheba Medical Center, Israel.

* **Corresponding Author:** Dr. Itamar Aroch, DVM, DECVIM-CA (Internal Medicine), Koret School of Veterinary Medicine, Hebrew University of Jerusalem, P.O. Box 12, Rehovot, 761001, Israel. Tel: 03- 9688556, Fax: 03-9604079. E-mail: itamar.aroch@mail.huji.ac.il

ABSTRACT

Hemophilia A (HA) is the most common inherited bleeding disorder in dogs. It is sex-linked, and has been described in many breeds. This report describes the clinical course and the diagnosis of HA in a 7-month old Parson Russell Terrier puppy, which was presented due to repeated bleeding episodes. The diagnostic tests included complete blood counts, prothrombin time (PT), activated partial thromboplastin time (aPTT), buccal mucosal bleeding time (BMBT), thromboelastometry using a surface contact activator (INTEM) and tissue factor (EXTEM) and determination of activities of factors VIII, IX and XI. The platelet counts, BMBT, PT and EXTEM were within reference intervals. The activities of factors VIII, IX and XI were 0.97%, 71.0% and 84.4%, respectively, compared to their average activities in the samples of two healthy dogs. Testing also ruled out the presence of coagulation inhibitors. The results confirmed a diagnosis of inherited HA, with severe factor VIII:C deficiency (<1% compared to reference plasmas). The aPTT, measured both by coagulometric analyzers and a fibrometer were prolonged (1.05- to 2.3-fold the upper reference limits [URL]), as was the INTEM clotting time (2.3-fold the URL), and did not reflect the severity of the deficiency. The dog was treated with oral tranexamic acid, which failed to prevent repeating bleeding episodes, and was therefore euthanized at his owners' request. This is the first report of HA in a Parson Russell Terrier in Israel, and the first report in which thromboelastometry was also utilized as a diagnostic test in HA in dogs.

Keywords: Canine; Coagulation; Hemostasis; Thromboelastometry; Factor VIII; Tranexamic Acid

INTRODUCTION

Hemophilia A (HA) is a hereditary, recessive, sex-linked bleeding disorder, almost exclusively affecting males, resulting from of a functional or quantitative factor VIII:C (FVIII:C) deficiency. The latter is a non-enzymatic protein, a crucial coenzyme for factor IXa, a serine protease, and together they form the intrinsic tenase, an important procoagulant complex, responsible for factor Xa generation, and subsequently conversion of prothrombin to active thrombin (1).

The disease is well described in humans, with over 2300 documented unique mutations in the factor VIII:C gene-

encoding (2, 3), however, limited information regarding such mutations is known in dogs (4, 5). It is the most common hereditary secondary clotting disorder in dogs, and may affect any dog breed (1, 6). It has been described in several dog breeds, including mixed breeds (mostly German Shepherd and Labrador retriever crosses), German Shepherd, Labrador and Golden retrievers, Boxer, Belgian Mallinois, Cocker Spaniel, Weimaraner, Miniature Poodle, American Pit Bull Terrier, Beagle, Dachshunds and Dachshund crosses, Parson Russell Terrier (also known as Jack Russell Terrier) and its crosses, West Highland White Terrier, German Shorthaired

Pointer, Australian Kelpie, Bassett Hound, Boston Terrier, Chihuahua, Chow-Chow, English Bulldog, Japanese Chin, Miniature Schnauzer, Pug-Beagle crossbred, Redbone Coonhound, Rhodesian Ridgeback, Rough Collie, Saint Bernard, Shih Tzu, Yorkshire Terrier, and Welsh Corgi (1, 6, 7-14). Based on the human criteria, in the largest survey study of the disease ($n = 39$), the severity of HA, based on FVIII:C deficiency, was mild (FVIII:C activity 6%-20% of the RI), moderate (2%-5%) and severe (<2%) FVIII:C deficiencies were recorded in 10, 13 and 16 dogs, respectively (7).

In most dogs with HA, the disease is diagnosed within one year of age, and all are diagnosed within 25 months. The initial clinical signs of HA mostly include spontaneous bruising or hematomas (38%), as well as excessive or unanticipated bleeding during elective surgical procedures, gingival bleeding during loss of deciduous teeth, bleeding after minor trauma, and spontaneous intra-cavity or organ bleeding, hematochezia, hematemesis, scleral hemorrhage and epistaxis. The most common bleeding sites are the subcutaneous tissue (67%), joints (51%) and gums (36%) (1, 6, 7).

The final diagnosis of HA is based on demonstrating FVIII:C deficiency as measured by activated partial thromboplastin time (aPTT), in which a 1:1 mixture of the suspect dog plasma and a commercial FVIII:C-deficient plasma is checked, compared to a similar mixture of a plasma pool, or plasma of normal healthy controls with the commercial FVIII:C-deficient plasma (6, 15).

CASE REPORT

A 7-month old, male pure-bred Parson Russell terrier, purchased from a breeder, was referred to the Hebrew University Veterinary Teaching Hospital (HUVTH) due to repeating bleeding episodes. Two months prior to presentation, a hematoma of 10-cm diameter was observed by the owners on the head after the dog had suffered from a minor trauma to the head. The hematoma was aspirated by the referring veterinarian, but recurred a day later, and was then left untreated, and resorbed within several days. One month later, with teething, profound bleeding was noted by the owners from the deciduous canine teeth, for four days, and melena was noted as well. A complete blood count (CBC) showed a regenerative anemia (hematocrit 21.3%, reference interval [RI] 37.3-61.7%; reticulocytes $249 \times 10^3/\mu\text{L}$, RI $10-110 \times 10^3/\mu\text{L}$). The platelet count was $204 \times 10^3/\mu\text{L}$ (RI $148-484 \times 10^3/\mu\text{L}$).

The prothrombin time (PT) was 12.2 sec (compared to 11.1 sec of a plasma pool). The activated partial thromboplastin time was 40 sec (compared to 20.1 sec of a plasma pool). The deciduous tooth where the bleeding was noted was extracted. The dog was prescribed omeprazole (10 mg PO q12h) and sucralfate (0.5 g PO q8h), due to suspected gastrointestinal bleeding, tranexamic acid (TXA; hexakapron, Teva, Petach-Tikva, Israel; 125 mg PO q12h, approximately 18 mg/kg) and oral ferrous-sulfate (dose and brand unknown). One month later, the dog was rechecked, and was without any abnormalities. Omeprazole and sucralfate were discontinued. Two days later, the dog was rechecked and seemed normal, and all medications were discontinued. Two days later, the dog was presented to the Hebrew University Veterinary Teaching Hospital (HUVTH). Physical examination was unremarkable. A CBC showed a mild macrocytic anemia (hematocrit 35.7%, RI 37.1-57%; mean corpuscular volume [MCV] 79.7 fL, RI 58.8-71.2 fL), and the platelet count was within the RI. Blood smear examination showed mild polychromasia, anisocytosis, hypochromasia and schistocytosis.

Coagulation times were first performed using an automated coagulometric analyzer (ACL-9000, Instrumental Laboratories, Milano, Italy). The PT was 11.1 sec (RI 6.0-9.0 sec), the aPTT was 20.4 sec (RI 11.5-19.5 sec) and fibrinogen concentration was 277 mg/dL (RI 150-300 mg/dL). The aPTT was repeated, and was 20.9 sec. Buccal mucosal bleeding time (BMBT) was 3 min and 20 sec (RI 1.7-4.2 min). Thromboelastometry (Rotem GmbH, Munich, Germany) was performed twice, once using a contact activator (INTEM) and once with tissue factor (TF) (EXTEM). The latter was unremarkable. The INTEM (Figure 1) showed a markedly prolonged clotting time (CT; 459 sec, RI 31-97 sec), while the maximal clot force (MCF) was mildly increased (75 mm, RI 42-70 mm), as were clot forces at 10 and 20 min (A10 and A20, respectively; Figure 1). The INTEM maximal lysis (ML) was increased (27%, RI 0-17%) as were the time to maximal velocity (MAXV-t), maximal clot elasticity (MCE) and the area under the curve (AUC) (Figure 1). Based on the historical bleeding episodes, the normal PT, BMBT and EXTEM, the markedly prolonged INTEM CFT and the prolonged aPTT as measured at the referring clinic, and despite the repeated automatically measured aPTTs at the HUVTH, which were only mildly prolonged, an inherited deficiency in one of the intrinsic coagulation

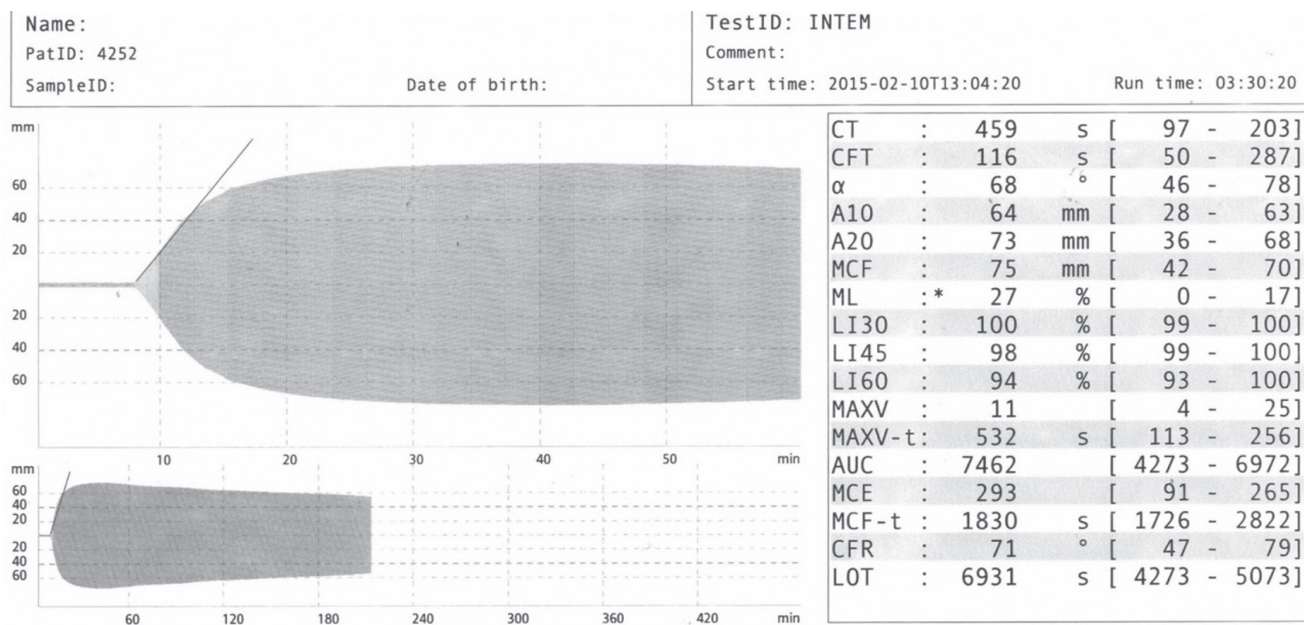


Figure 1: Thromboelastogram of a Parson Russell Terrier puppy with hemophilia A, using a contact activator (INTEM). Numeric data are presented on the right hand side, with reference intervals in parentheses. CT, clotting time; CFT, clot formation time; α , alpha angle; A10, clot force at 10 min.; A20, clot force at 20 min.; MCF, maximal clot force; ML, maximal lysis; LI30, LI45 and LI60, clot lysis at 30, 45 and 60 min., respectively; MAXV, maximal velocity; MAXV-t, time to maximal velocity; AUC, area under the curve; MCE, maximal clot elasticity; MCF-t, time to maximal clot force; CFR, clot formation rate; LOT, lysis onset time.

pathway factors, VIII:C, IX or XI, (hemophilia A, B and C, respectively) was suspected.

The aPTT was then measured twice using a fibrometer (KC-1 micro, Amelung, Lemgo, Germany), and results were 44.9 and 35.8 sec (RI 11.5-19.5 sec.). Plasma from the dog was then mixed 1:1 with citrated plasma obtained from a healthy staff-owned dog (in which the aPTT was 17.2 sec.), and the aPTT was repeated, using both the automated coagulometric analyzer and the fibrometer, and results were 15.9 and 20.5 sec., respectively. This confirmed that no coagulation inhibitors were present in the suspect dog's plasma which potentially might have led to prolonged aPTT.

The dog was discharged with oral TXA (125 mg q8h) treatment pending further tests. Two days later, the dog was represented to the HUVTH due to a large hematoma, of 10-cm in diameter in the jugular area, where the venipuncture was made in order to obtain blood samples during the prior visit. At that time, the packed cell volume was 40%, and the fibrometer aPTT was 41.7 sec.

Frozen citrated plasma from the suspect dog and from

two healthy staff-owned dogs (in which the aPTTs were within RI) that were used as reference samples, were sent to the Laboratory of Hemostasis, Institute of Thrombosis and Hemostasis, Chaim Sheba Medical Center, Israel, for measurement of coagulation factors VIII, IX and XI activities. Factor VIII, IX and XI activity levels in dog's plasma were measured by ACL TOP 500 analyzer (Instrumental Laboratories, Bedford, MA, USA), using SynthASil and factor VIII-deficient plasma, factor IX-deficient plasma and factor XI-deficient plasma, respectively (HemosIL, Instrumental Laboratories, Bedford, MA, USA). The activities of factors VIII, IX and XI of the dog were 0.97%, 71.0% and 84.4%, respectively, compared to their average activities in the samples of the two healthy dogs, thereby confirming presence of severe FVIII:C deficiency (HA). The owners were instructed to avoid strenuous activity, and TXA was prescribed.

Two weeks later, the dog swallowed a plastic bag, and was administered apomorphine intramuscularly by the referring veterinarian, and subsequently developed a large hematoma at the injection site. The dog was then euthanized at his owners'

request. The breeder was notified, but further inquiry was declined.

DISCUSSION

The present dog was suspected with an inherited coagulopathy based on its male sex and the typical clinical signs of repeated bleeding episodes, which have occurred when the dog was aged less than seven months, appeared at venipuncture sites, teething sites and one suspected bruising site, in agreement with previous reports of canine HA (1, 6, 7). Hemophilia A has been reported previously in the Parson Russell Terrier (7), but this is the first report of the disease in this breed in Israel. HA occurs on average in 50% of the males in a litter, while 50% of its females will be carriers, by breeding a carrier female with an affected male. Males with mild forms of hemophilia may survive to reproduce, and when bred, the mutation is transmitted to all his daughters, which will be carriers, but none of his sons will be affected (1). A full inquiry as to the dame, sire and littermates was warranted in this case. Since Parson Russell Terriers are becoming more popular in the country and because inbreeding may occur, local veterinarians and breeders should be aware of the possibility of occurrence of HA in the breed.

CBCs, performed at both the referring clinic and the HUVTH ruled out thrombocytopenia, while the BMBT ruled out thrombopathy. In addition, the PT results at both the referring clinic and the HUVTH, although very mildly prolonged compared to their RI (or compared to a plasma pool at the referring clinic), could not account for the repeating bleeding episodes in this dog, and ruled out inherited factor VII deficiency or common coagulation pathway clotting factor deficiency. Fibrinogen (Clauss) concentration was within RI, ruling out hypofibrinogenemia or dysfibrinogenemia. While the aPTT, measured by automatic coagulometric analyzers at both the referring clinic and at the HUVTH were prolonged, this prolongation was only 1.046 to 2-fold the upper reference limit (URL) (or compared to a plasma pool at the referring clinic), and did not reflect a severe inherited coagulopathy. Similarly, the aPTT measured by a fibrometer at the HUVTH, although prolonged, was only 1.84- to 2.30-fold the URL. It was therefore uncertain, based on these results, that hemophilia was indeed likely. A previous study has examined the relationship between the aPTT and FVIII:C concentration in 145 samples from

dogs with HA, and showed that although the correlation between the two was highly significant, the relationship could be proven most precisely by geometric regression, and not by a linear correlation (16). In other words, in a single hemophiliac dog, although plasma FVIII:C activity might be markedly low, the aPTT prolongation might not reflect it precisely in a linear manner. This might explain the mildly, unremarkably prolonged aPTTs in this case, although plasma FVIII:C activity was subsequently shown to be markedly low (<1% compared to healthy controls), and therefore supporting a severe form of HA.

In agreement with unremarkable prolongation of the aPTT, the thromboelastometry INTEM test did show a similar prolongation of the CT, which was 2.3-fold the URL, and the MAXV-t was 2-fold the URL as well. Interestingly, the INTEM measures of clot strength, (A10, A20 and MCF) as well as the MCE were mildly above their RI. The reason is unclear, and since these measurements were very near the URL in the EXTEM test, the clinical significance of these abnormalities is questionable. They might suggest that once formed, the clot force is adequate. This is supported by the increased AUC as well. The reason for the increased INTEM ML is unclear, but this was a mild increase, and its significance is questionable as well. Both the INTEM and EXTEM demonstrated that global coagulation was normal in the dog, excluding the prolonged INTEM CT. Thromboelastometry or thromboelastography test results have never been reported in dogs with HA, to our best knowledge, and this is the first report to do so. In hemophiliac humans, these tests are mostly utilized for monitoring individual patients during therapy, especially when inhibitors of coagulation are identified (17, 18), but we could not find evidence of such tests to be used in screening of humans with HA.

In human hemophiliacs, historical treatments included fresh frozen plasma (FFP), and later on, cryoprecipitate, which were later substituted with factor replacement therapy, first with virally-inactivated FVIII concentrates, and currently with several human recombinant FVIII products, or with bypass therapy (19-21). FVIII concentrates, recombinant FVIII and bypassing agents (i.e., recombinant factor VIIa and activated prothrombin complex concentrate [APCC]) are administered both for prophylaxis as and control of bleeding. These are unavailable for treatment of dogs, generally because such treatment is cost-prohibitive. Additionally, potentially, such treatment might result in development of anti-FVIII

(or anti-factor VIIa) antibodies, which will result in bleeding. Cryoprecipitate is also mostly unavailable in veterinary medicine due to cost issues. Therefore, similar prophylaxis is not practiced in hemophilic dogs, while treatment of bleeding is limited to FFP, whole blood and packed cells (7). Most dogs with HA suffer repeated bleeding episodes, and the main treatments reported included transfusion of FFP, whole blood and packed cells. In a survey of hemophilia A in 39 dogs, most dogs (56%) required a single transfusion or single yearly transfusions, and the rest received several transfusions. FFP was the most commonly used blood product (n = 22). Thirty-five dogs of these 39 dogs were treated, for up to eight years post-diagnosis, while four were euthanized at the time of the diagnosis or shortly thereafter. Of these 35 dogs, seven were subsequently euthanized due to the disease, five died due to bleeding, resulting from FVIII:C deficiency, while 18 were still alive and being treated at the time the survey was conducted (7). Treatment of dogs is therefore expensive, requiring long-term owner commitment, while the long-term prognosis must be guarded. In the present dog, due to several bleeding episodes over a relatively short time-period, and in light of the severe FVIII:C deficiency, the owners elected euthanasia, although the possibility that the dog could survive for a relatively long period was conveyed to them. In a previous survey of HA in dogs, 4/39 dogs were euthanized at the time the diagnosis of the disease was made (7). While the election of euthanasia in the present dog might be argued, since in this case FVIII deficiency was severe, repeated bleeding episodes were to be expected. In the above mentioned survey (7), 13/39 cases were defined as severe FVIIIa deficiency. Among these, 2 dogs were lost to follow-up. Four dogs of the remaining 11 cases (36%) were either euthanized or died within two years from the time the diagnosis of HA was made (7).

There are no reports on the use of TXA in dogs with HA, although it has been investigated in healthy dogs, and was found to be safe (27). In hemophilic humans with coagulation factor inhibitors, addition of TXA to treatment with recombinant human factor VIIa (rhFVIIa) or with APCC, resulted in clot stability normalization compared to healthy controls (22). Good to excellent results were achieved in 9/10 human HA patients undergoing surgery, or with bleeding, with bypassing agent (i.e., use of rhFVIIa or APCC which promote coagulation and 'bypass' the intrinsic coagulation pathway) and TXA treatment (23). Similar results were dem-

onstrated by thromboelastometry *in vitro* (24). The potential of TXA as a prophylactic agent against bleeding in hereditary coagulation disorders in human patients untreated with factor replacement or bypassing agent (i.e., rhFVIIa or APCC) therapy undergoing endoscopy was safe and beneficial in cases of mild to moderate coagulation disorders (25). Pre- and post-operatively administered TXA has also been used successfully with a single recombinant factor VIIa in preventing bleeding in humans with severe factor IX deficiency and inhibitors undergoing major surgeries (26).

To the best of the knowledge of the authors, there are no studies of TXA as a sole prophylactic agent in non-symptomatic hemophilic humans. In an uncontrolled retrospective study comparing the use of blood products in dogs with various, non-hemophilia bleeding disorders, it was concluded that TXA is safe, but there were no conclusive evidence as to its efficiency in reducing blood product transfusion requirements (27). In another study, evaluating the effect of intravenous TXA in healthy dogs on thromboelastographic measures, the results were unremarkable (28). In the present dog, no bleeding episodes were noted throughout the initial period in which the dog had been treated with TXA. When the venipuncture was made at the HUVTH the dog was not receiving any medications, and the procedure resulted in a hematoma in the jugular vein area. The dog was discharged later from the hospital with TXA treatment. However, despite this ongoing treatment, he developed a hematoma at an injection site later on. It is therefore impossible to draw any conclusion as to the effect of TXA treatment in this case. It was minor at best, or possibly, the drug had no beneficial effect. It would seem that with no additional bypassing agent or FVIII:C replacement therapy, oral TXA cannot prevent bleeding associated with minimally invasive procedures, such as venipuncture, in dogs.

In conclusion, this is the first report of HA in a pure-bred Parson Russell Terrier in Israel, and, to the best of our knowledge the first report of thromboelastometry measures in a naturally-occurring HA in dogs. Treatment with TXA failed to prevent bleeding in this case.

REFERENCES

1. Brooks, M.: Hereditary Coagulopathies. In: Weiss, D.J. and Wardrop, K.J. (Eds.): Schalm's Veterinary Hematology, 6th edition, Blackwell Publishing, Ames. pp. 661-667, 2010.
2. Rallapalli, P.M., Kembal-Cook, G., Tuddenham, E.G., Gomez, K.

- and Perkins, S.J. (2014) Factor VIII Varian Database, Royal Free London NHS, NHS Trust. Available at <http://www.factorviii-db.org/>. Accessed at May 15, 2015.
3. Cooper, D.N., Ball, E.V., Stenson, P.D., Phillips, A.D., Howells, K., Heywood, S., Mort, M.E. and Horan, M.P. The Human Gene Mutation Database at the University of Cardiff. Available at: <http://www.hgmd.org>. Accessed at May 15, 2015.
 4. Christopherson, P.W., Bacek, L.M., King, K.B. and Boudreaux, M.K.: Two novel missense mutations associated with hemophilia A in a family of Boxers, and a German Shepherd dog. *Vet. Clin. Pathol.* 43: 312-316, 2014.
 5. Mischke, R., Wilhelm, C.H., Czwalinna, A., Varvenne, M., Narten, K. and von Depka, M.: Canine hemophilia A caused by a mutation leading to a stop codon. *Vet. Rec.* 169: 496, 2011.
 6. Barr, J.W. and McMichael, M.: Inherited disorders of hemostasis in dogs and cats. *Top Compan. Anim. Med.* 27: 53-58, 2012.
 7. Aslanian, M.E., Sharp, C.R., Rozanski, E.A., de Laforcade, A.M., Rishniw, M. and Brooks, M.B.: Clinical outcome after diagnosis of hemophilia A in dogs. *J. Am. Vet. Med. Assoc.* 245: 677-683, 2014.
 8. Gavazza, A., Lubas, G., Trotta, M. and Caldin, M.: Hemophilia A in a Belgian Shepherd Malinois dog: case report. *Res. Vet. Sci.* 97: 96-98, 2014.
 9. Dunning, M.D., Averis, G.F., Pattinson, H., Targett, M., Cade, S. and Herrtage, M.E.: Haemophilia A (factor VIII deficiency) in a litter of Weimaraners. *J. Small Anim. Pract.* 50: 357-359, 2009.
 10. Brooks, M.B., Barnas, J.L., Fremont, J. and Ray, J.: Cosegregation of a factor VIII microsatellite marker with mild hemophilia A in Golden Retriever dogs. *J. Vet. Intern. Med.* 19: 205-210, 2005.
 11. Thompson, M.S. and Kreeger, J.M.: Acute paraplegia in a puppy with hemophilia A. *J. Am. Anim. Hosp. Assoc.* 35: 36-37, 1999.
 12. Brooks, M.B., Coccarri, P.J., Riback, S.C. and Joseph, S.A.: Hemophilia A in a German shorthaired pointer: clinical presentations and diagnosis. *J. Am. Anim. Hosp. Assoc.* 32: 25-28, 1996.
 13. Mansell, P.D., Parry, B.W. and Van Orsouw, P.J.: Haemophilia A in a family of miniature poodles. *Aust. Vet. J.* 67: 420-421, 1990.
 14. Parry, B.W., Holloway, S.A., Birch, D.J. and Mackin, A.J.: Haemophilia A in a cocker spaniel dog. *Aust. Vet. J.* 65: 326-327, 1988.
 15. Lubas, G., Caldin, M., Wiinberg, B.O. and Kristensen, A.T.: Laboratory Testing of Coagulation Disorders. In: Weiss, D.J. and Wardrop, K.J. (Eds.): *Schalm's Veterinary Hematology*, 6th edition, Blackwell Publishing, Ames. pp. 1082-1100, 2010.
 16. Mischke, R.: Influence of factor VIII:C and factor IX activity in plasmas of hemophilic dogs on the activated partial thromboplastin time measured with two commercial reagents. *Haemophilia* 6: 135-139, 2000.
 17. Furukawa, S., Nogami, K., Ogiwara, K., Yada, K., Minami, H. and Shima, M.: Systematic monitoring of hemostatic management in hemophilia A patients with inhibitor in the perioperative period using rotational thromboelastometry. *J. Thromb. Haemost.* doi: 10.1111/jth.12987, 2015.
 18. Fisher, C., Mo, A., Warrillow, S., Smith, C. and Jones, D.: Utility of thromboelastography in managing acquired Factor VIII inhibitor associated massive haemorrhage. *Anaesth. Intensive Care.* 416: 799-803, 2013.
 19. Sørensen, B. and Bevan, D.J.: A critical evaluation of cryoprecipitate for replacement of fibrinogen. *Br. J. Haematol.* 149: 834-843, 2010.
 20. Young, G., Mahlangu, J., Kulkarni, R., Nolan, B., Liesner, R., Pasi, J., Barnes, C., Neelakantan, S., Gambino, G., Cristiano, L.M., Pierce, G.F. and Allen G.: Recombinant factor VIII Fc fusion protein for the prevention and treatment of bleeding in children with severe hemophilia A. *Thromb. Haemost.* doi: 10.1111/jth.12911, 2015.
 21. Calvez, T., Chambost, H., Claeysens-Donadel, S., d'Oiron, R., Goulet, V., Guillet, B., Héritier, V., Milien, V., Rothschild, C., Roussel-Robert, V., Vinciguerra, C. and Goudemand, J.: Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A. *Blood.* 124: 3398-3408, 2014.
 22. Tran, H.T., Sørensen, B., Rea, C.J., Bjørnsen, S., Ueland, T., Pripp, A.H., Tjønnfjord, G.E. and Holme, P.A.: Tranexamic acid as adjunct therapy to bypassing agents in hemophilia A patients with inhibitors. *Haemophilia* 20: 369-375, 2014.
 23. Holmström, M., Tran, H.T. and Holme, P.A.: Combined treatment with APCC (FEIBA®) and tranexamic acid in patients with hemophilia A with inhibitors and in patients with acquired hemophilia A—a two-centre experience. *Haemophilia* 18: 544-549, 2012.
 24. Rea, C.J., Foley, J.H., Bevan, D.H. and Sørensen, B.: An in-vitro assessment of tranexamic acid as an adjunct to rFVIII or rFVIIa treatment in hemophilia A. *Ann. Hematol.* 93: 683-692, 2014.
 25. Davis, A., Walsh, M., McCarthy, P., Brown, G., Roberts, S., Tran, H., Street, A., Fong, C.Y. and Kemp, W.: Tranexamic acid without prophylactic factor replacement for prevention of bleeding in hereditary bleeding disorder patients undergoing endoscopy: a pilot study. *Haemophilia* 19: 583-589, 2013.
 26. Livnat, T., Tamarin, I., Mor, Y., Winckler, H., Horowitz, Z., Korianski, Y., Bar-Zakay, B., Seligsohn, U. and Salomon, O.: Recombinant activated factor VII and tranexamic acid are haemostatically effective during major surgery in factor XI-deficient patients with inhibitor antibodies. *Thromb. Haemost.* 102: 487-492, 2009.
 27. Kelmer, E., Marer, K., Bruchim, Y., Klainbart, S., Aroch, I. and Segev, G.: Retrospective evaluation of the safety and efficacy of tranexamic acid (hexakapron®) for the treatment of bleeding disorders in dogs. *Isr. J. Vet. Med.* 68: 94-100, 2013.
 28. Kelmer, E., Papashvilli, V., Rahimi-Levene, N., Bruchim, Y., Segev, G., Aroch, I. and Klainbart, S.: Effects of intravenous administration of tranexamic acid on hematological, hemostatic and thromboelastographic analytes in healthy adult dogs. *J. Vet. Emerg. Crit. Care.* 24: 455-460, 2014.