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BLEEDING DISORDERS IN ANIMALS

Hereditary Disorders

Fibrinogen (Factor I) Deficiencies

Hereditary fibrinogen deficiencies have been recognized in Saanen dairy goats in the Netherlands and several dog breeds (St. Bernards in West Germany; borzoi, vizsla and collie families in North America). These disorders can be caused by a complete lack of fibrinogen (afibrinogenemia), reduced fibrinogen (hypofibrinogenemia), or an abnormal fibrinogen (dysfibrinogenemia). These defects produce a mild to severe or fatal bleeding diathesis and have an autosomal inheritance pattern.

Prothrombin (Factor II) Deficiency

Prothrombin defects are caused by both hypoprothrombinemia and dysprothrombinemia. These are autosomal disorders that produce mild to moderately severe bleeding problems. The only inherited prothrombin abnormality recognized to date in animals occurred in a family of boxer dogs from Texas. The defect was characterized by epistaxis and umbilical bleeding in newborn puppies and mild mucosal surface bleeding in young adults. Prothrombin deficiency has also been reported in an English cocker spaniel.

Vitamin K-Dependent Coagulation Factor Deficiency

Combined deficiency of all vitamin K-dependent coagulation factor (II, VII, IX and X) has been reported in a family of Devon Rex cats. The feline disorder was vitamin K responsive and was inherited as an autosomal trait.

Factor VII Deficiency

Factor VII deficiency is commonly reported worldwide in beagle dogs from large commercial breeding colonies. The apparent high incidence in this breed probably reflects the widespread use of beagles in biomedical research. It has also been described in an Alaskan malamute, bulldogs, and mixed breeds. The disorder is usually discovered fortuitously during routine hematological screening for drug testing, research, or clinical workup. Canine factor VII deficiency is typically a mild disease with no overt bleeding tendency except for easy bruising.

Hemophilia A (Factor VIII:C Deficiency, Classic Hemophilia)

The most common of the severe inherited coagulopathies, hemophilia A occurs in humans, dogs, horses, sheep, cattle and cats. Mild, moderate, and severe forms of hemophilia have been recognized in humans and dogs, whereas the equine defect is usually severe and the feline defect tends to be mild. The canine disease has been reported in nearly every pure breed of dogs and in mongrels, but is most common in German shepherds worldwide having descended from the obligatory carrier progeny of an influential hemophilic stud. Smaller breeds tend to be less severely affected than larger breeds. Thoroughbred, standardbred, and quarter horses have been
reported with hemophilia, as have several breeds and mixed breeds of cats, Australian Hereford cattle and Dutch sheep.

Hemophilia is an X chromosome-linked recessive trait in humans and other animals. Affected males are hemizygous for the trait, whereas carrier females are heterozygous and affected females (the product of a hemizygous and heterozygous mating) are homozygotes. This disease results in males from a very low concentration of clotting factor VIII:C, whereas carrier females have amounts of factor VIII:C of about 40-60% of normal.

Hemophilia B (Factor IX Deficiency, Christmas Disease)

Hemophilia B, also an X chromosome-linked recessive trait, is less common than hemophilia A and occurs in humans, about 20 breeds of dogs, and several breeds of cats as well as mixed breeds. It occurs as a mild to moderate disorder of small dog breeds (e.g. Cairn terrier, American cocker spaniel, Shetland sheepdog, Scottish terrier, and French bulldog) and cats, and as a severe diathesis in larger breeds (e.g. black and tan coonhounds, St. Bernards, Alaskan malamutes, Old English sheepdogs, and German shepherds).

As in classic hemophilia, carrier females can be identified by reduced (40–60%) levels of factor IX, although affected males have all had less than 5% factor IX. It is important to perform accurate diagnostic tests to differentiate between the hemophilias as both disorders have markedly prolonged intrinsic system clotting tests. The plasma defect of hemophilia B is corrected by addition of fresh normal serum, whereas that of hemophilia A is not because serum contains factor IX but not FVIII:C activity.

von Willebrand’s Disease (vWD)

von Willebrand first described the complex, multifaceted syndrome known as vWD in humans in 1926. The disorder is usually more mild than the hemophilias, and primarily involves mucous membranes and skin, with gastrointestinal and urogenital bleeding and epistaxis as common symptoms. The prolonged bleeding time also results in excessive surgically induced hemorrhage. The most common inherited bleeding disorder of humans, vWD has been recognized in swine, more than 60 dog breeds, several breeds of cats, a quarterhorse family, and an inbred strain of laboratory rabbits. The affected breeds with a high prevalence of the gene are Doberman pinscher (80% prevalence), German shepherd, miniature schnauzer, golden retriever, Shetland sheepdog, basset hound, standard poodle, keeshond, rottweiler, dachshund, Scottish terrier, Manchester terrier, and Pembroke Welsh corgi. In other breeds, the disorder is either less prevalent or the true prevalence is unknown because too few animals have been studied.

By far the most common form of canine vWD is type 1, inherited as an autosomal, incompletely dominant trait with variable clinical and laboratory expression based on the degree of penetrance of the mutant gene. In four dog breeds, Scottish terriers, Chesapeake Bay retrievers, Shetland sheepdogs, and German wirehaired pointers, in Himalayan cats, and Poland-China swine, vWD is analogous to the autosomal recessive type 3 vWD of humans. Homozygous affected animals make no measurable von Willebrand factor (vWF) and exhibit a moderate to severe bleeding tendency, whereas heterozygotes are detected by laboratory tests only (reduced vWF antigen or activity) and are otherwise asymptomatic.

In addition to the more commonly recognized types 1 and 3 vWD, many variants exist and are classified as type 2 vWD. Examples include families of German shorthair pointer dogs, and quarterhorses. The nationwide genetic screening program for canine vWD begun by the author in 1980, has since tested about 30,000 Doberman pinschers, 12,000 Shetland sheepdogs, 9,000 golden retrievers, 8,000 Scottish terriers, 5,000 Pembroke Welsh corgis, 5,000 standard and miniature poodles, and several thousand miniature schnauzers, bassett hounds, Akitas.

In dogs, vWD is exacerbated by concurrent hypothyroidism, so that asymptomatic carriers may exhibit a bleeding tendency if they develop autoimmune thyroiditis and become hypothyroid, a common situation found in many breeds, but especially prevalent in Doberman pinschers. Furthermore, hypothyroid dogs may exhibit thrombocytopenia and associated mucosal surface bleeding. Clinical experience with use of thyroid supplement, which nonspecifically shortens the bleeding time in animals with inherited or acquired vWD and other platelet dysfunctions, has supported the efficacy, safety and low cost of this approach.

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Thyroid supplementation alone may suffice to control bleeding in mild to moderate vWD, a situation analogous to the use of desmopressin (DDAVP) or danazol to control bleeding in
humans and animals. Because of the important role of vWF in sustaining platelet adhesion, animals that are asymptomatic heterozygotes for vWD (as determined by reduced vWF:Ag), are at risk to express a bleeding tendency if some other hemostatic disorder develops (e.g. rodenticide toxicosis, thrombocytopenia, liver disease, hypothyroidism).

Factor X Deficiency

A rare coagulation disorder, canine factor X deficiency was first described in the early 1970s in a family of American cocker spaniels. Since then, factor X deficiency has been diagnosed occasionally in mongrel dogs and more recently in the Jack Russell terrier. Homozygotes and some heterozygotes have very low levels of factor X (<6% to 35%) and a clinically expressed bleeding disease, whereas most heterozygotes (40-70% factor X) are asymptomatic. Affected dogs with less than 20% factor X usually do not survive neonatal life. The exception was an affected mongrel puppy with 6% factor X that lived for nearly a year before experiencing a fatal bleeding episode. This disease mimics the "fading puppy syndrome," as severely affected pups are stillborn or fade and die in the first week or two of life. Necropsies show massive internal bleeding. Signs in adults are mild and referable to mucosal surfaces. Complete absence of factor X is thought to be a lethal mutation because of its central role in coagulation.

Factor XI (PTA) Deficiency

Factor XI deficiency is a rare disorder of humans, most of whom are of Jewish background. Clinical signs are mild (hematuria, bruising, epistaxis, menorrhagia) unless the patient is subjected to surgical procedures. Bleeding usually starts 12–24 hrs after surgery and can be severe and protracted. Lethal bleeding has also been reported after minor procedures such as biopsies and tonsillectomy. The disorder also occurs in Holstein cattle, English springer spaniels, great Pyrenees, and Kerry blue terrier dogs, and is clinically similar to that of humans.

Factor XII Deficiency (Hageman Trait)

Hageman trait is an asymptomatic coagulation deficiency recognized in humans, dogs, and quite commonly in cats. The first feline case was discovered fortuitously by prolonged screening tests of intrinsic clotting. It had less than 5% factor XII and died without progeny. The second case, also discovered by screening tests, had less than 1% factor XII and has provided several generations of progeny.

In addition to these defects, the absence of detectable biological or immunological factor XII is a normal phenomenon of a variety of other vertebrates and invertebrates, such as whales, birds (including the common domestic fowl and waterfowl), reptiles, and possibly fish.

Platelet Function Defects

a. Thrombasthenia (Glanzmann's Disease). This bleeding disease has an autosomal inheritance, and is characterized by major reduction in clot retraction, occasional mild thrombocytopenia, but normal platelet morphology. The bleeding diathesis is severe and of the purpuric type, and epistaxis is common and profuse. The first animal cases were discovered in 1967 in a family of otterhound dogs. Both homozygotes and heterozygotes could be identified by abnormalities in specific platelet function tests. Bleeding episodes can be triggered by stress events.

b. Thrombopathia. A group of inherited thrombopathias have been described in humans, fawn- hooded rats, basset hounds, spitz dogs, American cocker spaniels, Simmental cattle, and cats. The defect in fawn- hooded rats and American cocker spaniels is similar to that of human platelet storage-pool disease. Canine thrombopathia (CTP) is an autosomally inherited bleeding disorder of the basset hound and spitz dogs. These conditions produce a bleeding tendency primarily of mucosal surfaces and intrinsic to the platelet.

Other Defects
a. **Complement Deficiencies.** A variety of inherited complement deficiencies are recognized in humans, whereas only three known similar disorders have been seen in other species. These are C4 deficiency in guinea pigs and rats, C5 deficiency in mice, and C6 deficiency in hamsters and rabbits.

b. **Double Hemophilia (Hemophilia AB).** A planned cross-breeding study between dogs with hemophilia A and hemophilia B was undertaken to study possible linkage between these two X chromosome genes. Dogs with double hemophilia were readily produced, thus demonstrating that the loci for hemophilia A and B are located far apart on the X chromosome.

c. **Prekallikrein Deficiency (Fletcher Trait).** Prekallikrein activity has been recognized in apes, swine, guinea pigs, mice, goats, sheep, and horses but is absent or minimal in dogs, cats, cattle, rabbits, whales, ducks, and chickens. Fletcher trait has recently been described in dogs, and miniature and Belgian horses.

### Acquired Disorders

Acquired bleeding disorders are numerous and more common than the inherited deficiencies of clotting factors and platelets.

#### Platelet Function Defects

a. **Quantitative (Thrombocytopenias and Thrombocytosis).** The majority of chronic cases of thrombocytopenia are immune-mediated. Primary immunological thrombocytopenia, of unknown etiology, has been termed idiopathic thrombocytopenic purpura. The majority of cases, however, appear secondary to a variety of underlying conditions such as use of heparin or estrogens, thrombosis, neoplasia, viral diseases, vaccine-associated reactions, other drugs and chemicals. Non-immunological thrombocytopenias are less common and have a better prognosis than the immunological cases, if the causative agent for disease can be eliminated.

b. **Qualitative.** A group of diseases and a large number of drugs are known to produce thrombopathias. Most drugs act by inhibiting the adhesion of platelets to subendothelium (aspirin, which blocks platelet cyclic endoperoxides) and/or the platelet release reaction (phenylbutazone, sulfonamides, antiinflammatory drugs, ticlopidine, promazine tranquilizers). Drugs that interfere with platelet function are contraindicated or must be used with caution in animals moderately or severely affected with bleeding disorders. Similarly, elective surgery should be avoided during the viremic phase (3–10 days) after live virus vaccination or viral exposure.

The most common diseases causing platelet dysfunction are renal failure, uremia and liver disease. Less common causes are the dysproteinemias such as myelomas and macroglobulinemias and estrogen toxicity. The classic clinical case of uremic bleeding is that of the old dog with compensated chronic interstitial nephritis which has inflamed gums and chronic periodontal disease. Dentistry on such a patient frequently results in excessive and prolonged gingival bleeding.

#### Disseminated Intravascular Coagulation with Fibrinolysis

The combined syndrome of DIC and secondary fibrinolysis is an important acute, subacute, or chronic disease process of humans and other animals. The major causes include viral, bacterial, protozoal, and parasitic infections; neoplasia; obstetric complications; and miscellaneous conditions such as trauma, shock, laminitis, heat stroke, colic, burns, drowning, liver disease, and canine heartworm disease.

#### Liver Disease

As the liver is the primary site of clotting factor synthesis, acute or chronic generalized hepatic disease often results in a bleeding tendency.

#### Vitamin K Deficiency and Rodenticide Toxicity

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The vitamin K-dependent clotting factors (II, VII, IX, X) are reduced in rodenticide toxicity (accidentally ingested or from therapeutic overdosage), in malabsorption syndromes, and in sterilization of the gut by prolonged use of antibiotics. Diagnosis is confirmed laboratory clotting tests, and a corrective response to treatment with whole blood or plasma transfusion and/or treatment with vitamin K₁. The newer second-generation rodenticides are 20–50 times more potent and longer lasting (several weeks) than first-generation warfarin compounds.

Bibliography


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