Hemostatic Disorders in Feline Immunodeficiency Virus–Seropositive Cats

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The hemostatic function of 40 feline immunodeficiency virus (FIV) seropositive and 8 FIV and feline leukemia virus (FeLV) seropositive cats was evaluated and compared with reference values from 30 clinically healthy cats. The FIV-positive cats were divided into 3 groups: group I included asymptomatic carriers; group II comprised sick FIV-infected cats with illnesses not likely to influence the hemostatic system; and group III included FIV-positive cats with diseases potentially associated with coagulopathies. Platelet counts in FIV/FeLV-infected cats were significantly lower than in healthy cats ($P < .003$), whereas the differences in the 3 groups of FIV-positive cats were variable (group I, $P = .009$; II, $P = .05$; III, $P = .09$). Thrombocytopenia ($<145,000$ platelets/$\mu$L) was present in 4 FIV-positive and 3 FIV/FeLV-positive cats. Platelet aggregation induced by collagen (0.5 and 0.25 $\mu$g/mL), adenosine diphosphate (ADP) (1 and 0.6 $\mu$mol/L), and thrombin (0.4 and 0.25 IU/mL) was not significantly different from that of healthy cats. The plasma coagulation system was evaluated by measuring one-stage prothrombin time (OSPT), activated partial thromboplastin time (APTT), thrombin time, fibrinogen concentration, coagulation factor assays, fibrinogen and fibrin degradation products (FDP), and plasma exchange test. The OSPT was similar in FIV-seropositive cats and in the healthy control group. Cats with FIV infection, however, had markedly shorter clotting times than healthy cats when using a modified test method system ($P < .05$). In all groups of FIV-infected cats and in those with FIV/FeLV infection, APTT measured with 2 different commercially available tests, and a modified plasma assay was markedly prolonged compared with healthy cats (APTT1 and 2:3 modification: $P < .01$; APTT2: $P < .05$ except group III). In 22 of 40 cats with FIV and in 5 of 8 cats with FIV/FeLV infection, plasma samples were beyond the reference range. The thrombin time was also significantly prolonged in cats with FIV and FIV/FeLV infection ($P < .01$); values in 17 of 40 FIV-positive cats were above reference range. The mean fibrinogen concentration of cats with FIV and FIV/FeLV infection was higher than in the healthy control group ($P < .001$). Factor VIII activity of 4 cats with FIV infection was 1.5 times higher than that of healthy cats. Factor XII activity of 3 cats from a group of 20 cats with prolonged APTT was between 20% and 35%. Factor IX and XI activities ranged between 70% and 120%. The markedly prolonged APTT in 2 FIV-positive cats could be shortened considerably in a plasma exchange test using 20% feline pooled plasma. The alterations in the coagulogram of FIV-seropositive cats were not related to a clinical stage or concurrent diseases. A definite explanation of the distinct disorder within the intrinsic plasma coagulation system in FIV-infected cats was not found.

FIV and FeLV serology was performed using a commercially available ELISA test (Cite Combo, IDEXX Laboratories, Westbrook, ME). Cats with less intense color development in the ELISA were either tested repeatedly (twice in an interval of 2 months), or the diagnosis was confirmed by western blot. The FIV- and FeLV-seropositive cats were client-owned patients of the Clinic of Small Animals, and were thus in different stages of infection (Table 2). FIV-positive cats were divided in three groups: group I included asymptomatic cats, group II comprised FIV-seropositive cats with illnesses not likely to induce hemostatic abnormalities (eg, gingivitis, diarrhea, skin disease), and group III included FIV-infected cats with concurrent diseases that may be associated with coagulopathies (uremia, liver disease, neoplasia, etc). Platelet-rich plasma (PRP) for platelet aggregation was obtained by centrifuging citrated blood at 80g and 20°C in a centrifuge (Beckman GPKR, Beckman Instruments, Munich) for 10 minutes. Centrifugation for 15 minutes at 2500g resulted in platelet-poor plasma (PPP). PRP was diluted with PPP to a platelet number of 300,000/$\mu$L. In case of a lower platelet count, undiluted PRP was used for platelet aggregation. Until testing, aliquots of frozen PPP were stored at $-70^\circ C$.

Materials and Methods

Cats and Sample Collection

Cats were considered healthy based on a normal physical examination, a hemogram within the reference range, and a negative enzyme linked immunosorbent assay (ELISA) for FIV and FeLV. Healthy cats were presented to the clinic for vaccination or neutering. Blood was collected from the jugular or cephalic vein from 30 healthy cats, 40 FIV-positive cats and 8 cats with concurrent FIV and FeLV infection. Table 1 lists age, breed, and gender of the cats evaluated. A small aliquot of blood (0.5 mL) was collected in a tube containing edetic acid (EDTA) for platelet counting and hemogram. The remainder of the sample (6 mL) was added to a tube containing 3.8% sodium citrate (blood/anticoagulant = 10:1) for aggregation studies and coagulation assays.

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Table 1. Distribution of Breed, Gender, and Age of the Cats Evaluated

| Breed                | No. (Healthy %) | No. FIV Seropositive (%) | No. FIV/FeLV Positive (%) |
|----------------------|-----------------|--------------------------|--------------------------|
| Domestic Shorthair   | 26 (87)         | 38 (95)                  | 7 (87.5)                 |
| Persian              | 2 (7)           | 0 (0)                    | 1 (12.5)                 |
| Siamese              | 1 (3)           | 2 (5)                    | 0 (0)                    |
| Norwegian Forest     | 1 (3)           | 0 (0)                    | 0 (0)                    |

| Gender               | No. (Healthy %) | No. FIV Seropositive (%) | No. FIV/FeLV Positive (%) |
|----------------------|-----------------|--------------------------|--------------------------|
| Male                 | 13 (43)         | 11 (27.5)                | 3 (27.5)                 |
| Male, neutered       | 0 (0)           | 18 (45)                  | 3 (27.6)                 |
| Female               | 17 (67)         | 7 (17.5)                 | 2 (25)                   |
| Female, neutered     | 0 (0)           | 4 (10)                   | 0 (0)                    |

| Age (y)              | Mean            | Median                    | Range                     |
|----------------------|-----------------|----------------------------|---------------------------|
| Male                 | 1.8             | 6.1                       | 3.8                       |
| Male, neutered       | 1.0             | 6.3                       | 4.0                       |
| Female               | 0.9±3.0         | 0.3–11.5                  | 0.5–7                     |
| Female, neutered     | 1.0             | 3.5                       | 0.5                       |
| Age (y)              | 2.0             | 8.5                       | 6.5                       |

After incubation in a water bath for 30 minutes at 37°C, the glass tube for quantification of fibrinogen and fibrin degradation products (FDP) was centrifuged at 1500g for 10 minutes, and the serum was stored at -70°C until further testing.

**Platelet Counts**

A 20-µL capillary tube was filled with EDTA-anticoagulated blood and placed in a Thrombo plus (Sarstedt, Nümbrecht, Germany) tube after 2 minutes; the platelets were then counted in a hemacytometer within 3 hours of sample collection.

**Platelet Aggregation Studies**

Platelet aggregation studies were performed with an Automated Platelet Aggregation and Coagulation Tracer (APACT) (Labor, Ahrensburg, Germany) within 3 hours of venipuncture. PRP was adjusted to 100% light transmission and PPP to 10% transmission. PRP (200 µL) was incubated for 30 seconds at 37°C and then aggregation was started by adding 10 µL of an agonist. The following agonists were used: collagen (0.25 and 0.5 µg/mL; Kollagenreagens Horm, Hormon-Chemie, Munich, Germany), Adenosinediphosphate (ADP) (0.6 µmol/L; Sigma Diagnostics, St. Louis, MO) and thrombin (0.25 and 0.4 IU/mL; Test-Thrombin, Behringwerke, Marburg, Germany).

**Coagulation Tests**

One-stage prothrombin time (Quick time, OSPT) and activated partial thromboplastin time (APTT) were measured with reagents of different manufacturers in healthy and FIV-seropositive cats (OSPT reagent 1 [OSPT1; Calcium-Thromboplastin; Behringwerke, Marburg, Germany (thromboplastin extract from human placentas)]; APTT reagent 1 (APTT1; Pathothrombin; Behringwerke, Marburg, Germany (lipid extract from human placentas with kaolin); OSPT reagent 2 (OSPT2; Hepato Quick; Behringer Mannheim, Mannheim, Germany) and APTT reagent 2 (APTT2; PTT-Reagenz; Bohrer Mannheim, Mannheim, Germany [cephalin and kaolin]). Additionally, plasma was diluted with diethylbarbiturate acetate buffer solution (Behringwerke, Marburg, Germany) 1:3 and 1:4 for OSPT1, and 2:3 for APTT1.

Thrombin time (TT; Thrombin-Reageuz; Bohringer Mannheim, Mannheim, Germany) and fibrinogen concentration (Fibrinogen-Reagenz, Bohringer Mannheim, Mannheim, Germany) were measured following the manufacturer's recommendation with a Schreiber and Gross coagulometer (Amelung, Lemgo, Germany).

**Factor Assay.** Factors VIII and XII (Bohringer Mannheim, Mannheim, Germany), and IX and XI (Behringwerke, Marburg, Germany) activities were measured in FV-positive cats after 1:40 dilution with DBA or imidazole buffer (Behringwerke, Marburg, Germany) and compared with a standard curve of pooled plasma from 10 healthy cats.

**Fibrinogen and Fibrin Degradation Products (FDP test; Bohringer Mannheim, Mannheim, Germany).** Serum was serially diluted from 1:1 to 1:64 with glycine buffer. Ten-microliter aliquots of diluted serum and latex suspension were gently mixed on a test card and evaluated for agglutination 2 minutes later. The highest dilution with clear agglutination was considered as the agglutination titer.

**Plasma Exchange Test.** Citrated plasma (0.2 mL) from FIV-infected cats with highly prolonged APTT were replaced by 0.04, 0.10, and 0.16 mL of pooled plasma of healthy cats and the APTT determined.

**Statistical Analysis.** The nonparametrical Kruskal-Wallis analysis of variance was used to compare the platelet count and the coagulogram (screening tests, fibrinogen) of 3 groups of FIV-seropositive cats, FeLV/FIV-infected cats, and healthy controls.

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**Table 2. Clinical Stages of FIV Infection in Cats**

| Clinical Stage          | No. | Clinical Signs in Cats in This Study |
|-------------------------|-----|-------------------------------------|
| Acute phase             | 0   | Lymphadenopathy, 3; Femoral fracture, 3; Tibial fracture, 1 |
| Asymptomatic carrier    | 7   | Upper respiratory tract infection, 6; renal failure, 5; skin disease, 4; gingivitis, 3; liver disease, 2; diarrhea, 2; cystitis, 2; vomiting, 1; neurological disorder, 1; neoplasia, 1 |
| AIDS-Related Complex    | 27  | Neoplasia, 2; anemia, 2; liver disease, 1; renal failure, 1 |
| AIDS phase              | 6   | Neoplasia, 2; anemia, 2; liver disease, 1; renal failure, 1 |

(Clinical staging according to Ishida and Tomoda.)

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(Clinical staging according to Ishida and Tomoda.)
HEMOSTASIS IN FIV-POSITIVE CATS

Table 3. Coagulation Parameters in Healthy Cats

| Parameter           | No. of Cats | Mean ± SD | Median (X ± 2s) |
|---------------------|-------------|-----------|----------------|
| Platelets (10^3/μL) | 30          | 357 ± 106 | 270            |
| OSPTI (s)*          | 30          | 8.5 ± 0.6 | 8.6            |
| APTT1 1:3           |             |           |                |
| modification (s)†    | 30          | 12.6 ± 1.5| 11.0           |
| OSPT1 1:4           |             |           |                |
| modification (s)‡    | 30          | 14.8 ± 2.0| 12.6           |
| OSPT2 (s)³          | 14          | 21.4 ± 3.1| 21.8           |
| APTT1 (s)*          | 30          | 16.8 ± 1.5| 21.2           |
| APTT1 2:3           |             |           |                |
| modification (s)³    | 30          | 22.7 ± 3.1| 37.6           |
| APTT2 (s)³          | 17          | 12.0 ± 0.7| 14.9           |
| TT (s)              | 30          | 16.3 ± 1.1| 17.8           |
| Fibrinogen (mg/dL)  | 30          | 168 ± 57  | 415            |

Abbreviations: APTT, activated partial thromboplastin time; DBA, diethylbarbiturate acetate; OSPT, one-stage prothrombin time.

Figures are beyond the reference range in 22 FIV-positive cats. Five plasma samples of FIV/FeLV-seropositive cats were also beyond the reference range for APTTI.

Discussion

Reports on coagulation disorders during the course of FIV infection in cats are rare, probably because hemorrhagic diatheses occur infrequently. Only Grindem et al. briefly described bleeding disorders in FIV-seropositive cats. An FIV-positive cat with leukopenia and thrombocytopenia associated with gastrointestinal bleeding was described by Friend et al.

Published reference ranges for platelet counts in normal cats are variable. The reference range in our study in 30 healthy cats (145,000 to 569,000/μL) is similar to those reported by others. However, other investigators have reported ranges of 300,000 to 800,000 platelets/μL. Thrombocytopenia plays an important role in various infectious diseases and also occurs in cats with FIV infection. In our study, 4 of 40 FIV-seropositive cats (10%) were thrombocytopenic (<145,000/μL). According to Shel-
Table 4. Coagulation Parameters in FIV- and FIV/FeLV-Seropositive Cats

| FIV-Seropositive Cats (Group I)* | FIV-Seropositive Cats (Group II)+ | FIV-Seropositive Cats (Group III)* | FIV/FeLV-Seropositive Cats |
|----------------------------------|-----------------------------------|-----------------------------------|-----------------------------|
| Mean ± SD                        | Mean ± SD                         | Mean ± SD                         | Mean ± SD                   |
| Platelets (10^3/pL)              | Platelets (10^3/pL)               | Platelets (10^3/pL)               | Platelets (10^3/pL)         |
| 309 ± 150                        | 284 ± 100                         | 278 ± 108                         | 308 ± 108                   |
| 8.6 ± 0.8                        | 8.7 ± 0.5                         | 8.8 ± 0.7                         | 8.8 ± 0.5                   |
| 11.4 ± 1.4                       | 11.4 ± 1.0                        | 11.4 ± 1.4                        | 11.6 ± 1.4                  |
| 12.5 ± 1.6                       | 13.0 ± 1.3                        | 12.9 ± 1.7                        | 13.4 ± 1.3                  |
| 21.6 ± 1.8                       | 22.3 ± 4.8                        | 19.4 ± 2.0                        | 21.4 ± 1.5                  |
| 33.7 ± 28.8                      | 24.7 ± 15.3                       | 35.8 ± 27.6                       | 37.5 ± 31.8                 |
| 44.4 ± 28.3                      | 33.3 ± 16.9                       | 46.3 ± 26.2                       | 45.4 ± 29.6                 |
| 64.4 ± 5.0                       | 19.0 ± 86.7                       | 21.8 ± 72.6                       | 23.0 ± 84.8                 |
| 17.7 ± 1.0                       | 19.8 ± 4.1                        | 18.6 ± 15.4                       | 18.3 ± 12.8                 |
| 362 ± 119                        | 353 ± 172                         | 460 ± 322                         | 382 ± 138                   |
| (dL)                             | (dL)                              | (dL)                              | (dL)                        |
| 7                                | 20                                | 13                                | 8                           |
| 188-633                          | 205-490                           | 33-453                            | 181-226                     |
| 8.6-9.9                          | 7.6-9.5                           | 8.0-10.4                          | 8.8-9.9                     |
| 9.8-13.8                         | 9.3-13.1                          | 9.7-13.9                          | 11.0-11.9                   |
| 10.6-14.9                        | 10.3-15.4                         | 10.6-15.8                         | 13.3-13.7                   |
| 19.3-23.6                        | 18.8-31.9                         | 15.3-21.5                         | 21.6-15.3                   |
| 13.8-86.6                        | 13.8-83.2                         | 14.6-98.5                         | 23.0-15.3                   |
| 21.7-101.5                       | 19.0-86.7                         | 18.8-119.1                        | 32.5-15.0                   |
| 12.4-25.1                        | 10.6-16.9                         | 11.6-19.1                         | 13.9-3.0                    |
| 15.7-19.2                        | 15.4-31.8                         | 15.0-24.4                         | 13.1-10.0                   |
| 415                               | 354                               | 460                               | 382                         |
| 221-495                          | 131-840                           | 188-1,416                         | 390-161                     |

Abbreviations: APTT, activated partial thromboplastin time; FeLV, feline leukemia virus; FIV, feline immunodeficiency virus; OSPT, one-stage prothrombin time.

OSPT1 (Calcium-Thromboplastin), undiluted plasma.

OSPT1, 1:3 plasma dilution with DBA buffer solution.

OSPT1, 1:4 plasma dilution with DBA buffer solution.

OSPT2, (Hepato Quick), undiluted plasma.

APTT1 (Pathromtin), undiluted plasma.

APTT1, 2:3 plasma dilution with DBA buffer solution.

FIV-seropositive asymptomatic cats.

FIV-seropositive cats with diseases not influencing the hemostatic system.

FIV-seropositive cats with illnesses potentially associated with coagulopathies.
HEMOSTASIS IN FIV-POSITIVE CATS

Collen et al., the prevalence of thrombocytopenia in FIV-positive cats is 6%. A mild thrombocytopenia (>100,000 and <150,000 platelets/μL) was found by other investigators in 16% of FIV-infected cats. A third report only mentioned one thrombocytopenic cat among 46 FIV-seropositive cats. In only one cat, thrombocytopenia was associated with a spontaneous bleeding disorder. In our study, 3 of 8 FIV/FeLV-seropositive cats (37.5%) were thrombocytopenic. In addition to platelet count, platelet function is vital for healthy cats.

Table 5. Platelet Aggregation in Healthy and FIV-Seropositive Cats

| Aggregation Agonist | No. of Cats | Aggregation-Maximum (%) | Aggregation-Gradient (%/min) |
|---------------------|------------|-------------------------|-----------------------------|
| Healthy             | FIV Seropositive |                       |                             |
| Collagen (0.5 μg/mL, Kollagenreagens Horm) | 13 | 89.9 | 108 |
| Collagen (0.25 μg/mL, Kollagenreagens Horm) | 3 | 90.4 | 90.3 |
| ADP (1 μmol/L)     | 6 | 89.2 | 125.3 |
| Thrombin (0.4 IU/mL, Test-Thrombin) | 5 | 97.8 | 91.3 |

Abbreviation: FIV, feline immunodeficiency virus.

The published reference ranges for the APTT vary considerably when using the same test system but different devices. Gentry and Cooper evaluated 4 reagents and found remarkable differences. However, the authors regarded all of the reagents tested as useful in the diagnosis of severe coagulation disorders. Both reagents evaluated in our study resulted in different reference ranges (14 to 20 seconds for APTT1 and 11 to 14 seconds for APTT2). The use of plasma dilutions is recommended when evaluating the APTT in cats. To improve sensitivity compared with undiluted plasma in healthy cats, the plasma sample in our study only needed to be diluted in a ratio of 2:3 for APTT1.

In vitro alterations in the intrinsic coagulation system were detected in 55% of FIV-infected cats in our study. They were characterized by a prolongation of the APTT, which was similar for both test reagents (APTT1, 2) and for the modified test assay of APTT1, which is more sensitive than APTT2. However, dilution did not provide additional benefit when evaluating the APTT. The TT evaluates the generation of fibrin from fibrinogen after the addition of thrombin. It is influenced by heparin, FDPs, and severe dysfibrinogenemia or hypofibrinogenemia. The reference ranges for the TT vary considerably, depending on the thrombin concentration used. Our reference ranges were similar to those published in the literature.

The fibrinogen concentration quantified using the method of Clauss yielded reference ranges of 54 to 282 mg/mL. This reference range is similar to that published by other authors (50 to 310 mg/dL). Hyperfibrinogenemia has not been previously reported in FIV- and FIV/FeLV-seropositive cats. Yet, this is common in cats with inflammatory diseases. Because the Claus method only detects functional, clottable fibrinogen, it is unlikely that dysfibrinogenemia accounted for the prolonged TT.

Isolated prolongation of the APTT may be caused by a clotting factor deficiency in the intrinsic pathway. Deficiencies of factors VIII, IX, XI, and XII have been reported in cats. Hemophilia A (factor VIII deficiency) is associated with a marked prolongation of the APTT. However, in this study F VIII activity was elevated (>120%) in 13 of the 20 FIV-positive cats (65%) in which it was evaluated. This is likely a reflection of the fact that F VIII is an acute phase reactant, and its plasma activity increases in the course of inflammatory processes.

Factor IX deficiency (hemophilia B) is also associated with a prolongation of the APTT in the cat, but a particularly marked prolongation of this screening test occurs in...
combined factors IX and XII deficiencies (>100 s).\textsuperscript{81,82} Factor IX-activity of the FIV-seropositive cats evaluated was within the reference ranges and did not cause the abnormality in the hemostatic system.

Previous reports suggest that F XIII deficiency is relatively common in healthy cats.\textsuperscript{63,71} However, in most of these, F XII activity is below 5%. Therefore, the F XII activity of 20% and 30% in 3 FIV-positive cats in this study is not likely to explain the prolongation of the APTT.

Circulating FDPs appear to be common in cats with DIC.\textsuperscript{2,4} High concentrations of circulating FDPs (>100 µg/dL) may cause prolongation of the APTT in humans.\textsuperscript{84,85} It is unlikely that the concentration of FDPs in FIV-infected cats in this study was a consequence of DIC. Moreover, these concentrations were probably not high enough to effect the APTT.\textsuperscript{42,45}

A plasma exchange test was performed in 2 FIV-seropositive cats with markedly prolonged APTT to elucidate this coagulation disorder. In humans, circulating inhibitors of coagulation occur in various diseases.\textsuperscript{86,89} Progressive inhibitory antibodies that exert an effect after 1 to 4 hours of plasma incubation are distinguished from direct inhibiting agents with immediate action.\textsuperscript{86} They can inhibit single coagulation factors (eg, F VIII or IX) or cause prolongations of the APTT or OSPT. The antibodies, usually immunoglobulin (Ig)G or IgM, interfere with phospholipids involved in the coagulation process. However, despite the prolonged clotting times, spontaneous bleeding occurs only when concurrent thrombocytopenia or factor deficiency exist.\textsuperscript{89}

There is only one report of a coagulation disorder induced by circulating inhibitors to F XI in a cat.\textsuperscript{74} Mixing of normal pooled plasma with the patient’s plasma (with and without incubation for 1 hour) resulted in a slow normalization of the APTT, and gradual increases of F XI activity is below 20% and 30% in FIV-infected cats. Moreover, these concentrations were probably not high enough to effect the APTT.\textsuperscript{42,45}

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