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Clinical Findings and Survival in Cats Naturally Infected with Feline Immunodeficiency Virus

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Background: The clinical course and outcome of natural feline immunodeficiency virus (FIV) infection are variable and incompletely understood. Assigning clinical relevance to FIV infection in individual cats represents a considerable clinical challenge.

Objective: To compare signalment, hematologic and biochemical data, major clinical problem, and survival among client-owned, FIV-infected, and uninfected domestic cats.

Animals: Client-owned, domestic cats tested for FIV (n = 520).

Methods: Retrospective, case control study. Logistic regression analyses were conducted to identify risk factors for FIV infection and to compare hematologic and biochemical data between cases and controls, after adjusting for potential confounders. Survival times were compared using Kaplan–Meier curves.

Results: The prevalence of FIV infection was 14.6%. Mixed breed, male sex, and older age were risk factors for FIV infection. Hematologic abnormalities, biochemical abnormalities or both were common in both FIV-infected and uninfected cats. Lymphoid malignancies were slightly more common in FIV-infected than uninfected cats. Survival of FIV-infected cats was not significantly different from that of uninfected cats.

Conclusions and Clinical Importance: Multiple hematologic and biochemical abnormalities are common in old, sick cats regardless of their FIV status. Their presence should not be assumed to indicate clinical progression of FIV infection. A negative effect of FIV on survival was not apparent in this study.

Key words: Clinicopathological findings; Feline immunodeficiency virus; Survival.

Feline immunodeficiency virus (FIV) is a common pathogen of domestic cats worldwide.[1] The number of FIV-infected pet cats in the United States alone is estimated to exceed 2.5 million.[2,3] Most natural infections likely result from intercat aggression, whereas transmission from queens to kittens and between cats within stable, closed households seems to be rare.[4,5] Risk factors for infection, including male sex, intact status, outdoor access, increasing age, and concurrent health problems are well documented.[2,4,6]

Feline immunodeficiency virus is closely related to human immunodeficiency virus (HIV) with regard to its morphology, in vitro characteristics, and elements of its pathogenesis.[1] In cats experimentally infected with FIV, progressive aberrations in multiple parameters of immune function, such as lymphocyte subset counts and mitogen responsiveness, have been documented.[7] Interestingly, these changes are rarely associated with clinical signs. This may be attributed to limited exposure to secondary and opportunistic pathogens in a minimal disease setting, genetic characteristics of the host or the dose, and strain of the infecting inoculum.

Abbreviations:

AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
FeLV	feline leukemia virus
FIV	feline immunodeficiency virus
HIV	human immunodeficiency virus
IFA	indirect immunofluorescence assay
IQR	interquartile range
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
OR	odds ratio
PCR	polymerase chain reaction
95% CI	95% confidence interval

Disease in HIV-infected humans without access to antiretroviral treatments is quite predictable, progressing through well-defined clinical stages: acute phase, asymptomatic carrier, persistent generalized lymphadenopathy, acquired immunodeficiency syndrome (AIDS)-related complex, and AIDS. The median time to the onset of the terminal AIDS stage is 8–10 years.[8] This stage is characterized by "AIDS-defining" illnesses, many of which are rare except in the face of profound immunosuppression (eg, *Pneumocystis* pneumonia). Disease staging includes consideration of the patient's CD4 + lymphocyte count which, together with plasma viral load, provides a surrogate marker to predict clinical outcome.[9]

The clinical course of FIV infection, on the other hand, is less well characterized or predictable. Attempts at clinical staging of FIV-infected cats have been attempted but not widely adopted.[10] A wide range of clinical signs has been reported in cats naturally infected with FIV, including oral disease, persistent cytopenias, immune-mediated disease, unexplained

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wasting, atypical, refractory or recurrent infections, and neurologic signs.[4,11] However, few of these signs have been demonstrated to be significantly different from those of control populations. With the exception of a subset of lymphomas, AIDS-defining illnesses are not recognized for FIV.[12] Furthermore, some FIV-infected cats remain asymptomatic with a normal life expectancy.[5]

The challenge for the clinician faced with a sick, FIV-infected cat is determining whether the virus is contributing to the current clinical signs. Studies comparing clinicopathological findings and outcomes between cats infected with FIV and appropriate control groups can inform our understanding of the consequences of natural infection, but such studies are limited.[13–18] The aims of this study were to compare the hematologic and biochemical changes, major clinical problem, and survival between groups of client-owned, FIV-infected and uninfected cats. Prevalence and risk factors for FIV infection also were determined.

Materials and Methods

Source of Data

The medical records of the Valentine Charlton Cat Centre, University of Sydney, were searched, using the terms FIV and feline immunodeficiency virus, for FIV testing results recorded between January 2005 and October 2009. The clinical indication for retrovirus testing had been determined by the attending clinician.

FIV and Feline Leukemia Virus (FeLV) Testing

Serology for FIV and feline leukemia virus (FeLV) was performed using commercial kits.[a,b] Polymerase chain reaction (PCR) testing for FIV was carried out at a commercial laboratory.[c] The sensitivity and specificity of this assay have been estimated to be 85–95% and 94–96%, respectively.[19] The FeLV indirect immunofluorescence assay (IFA) was performed at a commercial laboratory.[d]

Case and Control Definitions

A cat was defined as "FIV-infected" if it tested seropositive for FIV and had not been vaccinated,[e] as determined from the medical record or direct owner communication. A cat was considered to be "FIV-uninfected" if it tested seronegative or it tested seropositive and had been vaccinated but had returned a negative result on FIV PCR testing. FIV seropositive, vaccinated cats with unknown PCR status and seropositive cats with unknown vaccination and PCR status were excluded. A FeLV antigen test was considered to be positive if a positive result on in-house testing was confirmed by IFA, or the cat was in contact with an antigenemic cat.

Data Collection

Information obtained from the medical record including breed, sex, neuter status, date of FIV testing, FeLV antigen status (where tested), and date of death were recorded for FIV-infected (n = 76) and FIV-uninfected (n = 444) populations. The first hematologic and biochemical data, performed by Veterinary Pathology Diagnostic Services, University of Sydney, subsequent to FIV testing were recorded for FIV-infected cats (n = 75, data unavailable for 1 cat) and a subset of the control population (n = 231) that was selected using random numbers.[f] The median time lag between testing and hematologic and biochemical data collection was 0 days for both FIV-infected and control groups (FIV infected; range, 0–4179 days; interquartile range [IQR], 179; uninfected; range, 0–232 days; IQR, 1). The major clinical problem in these cats was assigned to 1 of 10 categories: cardiorespiratory, endocrine, gastrointestinal, genitourinary, healthy, immune-mediated, infectious, neoplasia, neurologic or not determined. Within the neoplasia category, the prevalence of lymphoid versus other malignancies was determined.

Data Analysis

Statistical software was used for all analyses.[g] All P values were 2-sided and considered significant at $<.05$. For risk factor and survival analyses, data from 520 cats were used, 76 infected cats and 444 uninfected controls. For analysis of analytes, data from 306 cats were used, 75 infected cats and 231 uninfected controls. Descriptive analyses were conducted to understand the distribution of variables and their preliminary association with FIV status.

Three sets of logistic regression analyses then were performed. The 1st set of analyses was conducted to identify any association between "FIV status" and the demographic factors "breed", "sex", "neuter status", and "age at FIV testing". Similar logistic regression analyses were conducted to evaluate the association between "FIV status" and hematologic and biochemical variables. To further compare the hematologic and biochemical data between FIV-infected and control cats, each hematologic and biochemical value was classified as decreased, normal or increased for each cat and a 3rd set of logistic regression analyses was conducted to compare analyte concentrations between FIV-infected and uninfected cats. Age and sex of cats were considered potential confounders and forced into the models for hematologic and biochemical variables, even if not significant. Univariable and multivariable model building was performed [http://sydney.edu.au/vetscience/biostat/macros/multi_about.shtml].[20]

The major clinical problem was compared between FIV-infected cats and the control sample using the 2-tailed Fisher's exact test. The only FeLV antigenemic cat had lymphoma and was excluded from analysis of major clinical problem.

Two survival analyses using the Kaplan–Meier approach were conducted to compare survival between FIV-infected and uninfected cats. The 1st analysis compared the age at the time of data collection (ie, date of death or censoring − date of birth) whereas the 2nd analysis compared survival time at the time of data collection (ie, date of death or censoring − date of testing). All surviving cats were censored at the date of their last visit to the clinic or at the time of data collection (August 17, 2010), whichever was earlier. Log rank test was used for comparisons.

Results

FIV and FeLV Testing

Five hundred twenty-five cats were tested for FIV during the study period. Seventy-six FIV seropositive cats that had not been vaccinated against FIV were considered to be FIV-infected. Five cats that tested seropositive for FIV but with undetermined vaccination status tested negative on PCR and were considered to be FIV-uninfected. The infection status

of 5 FIV seropositive cats could not be determined and they were excluded. The 439 cats that were seronegative were considered to be FIV-uninfected. In total, 76 FIV-infected cats and 444 FIV-uninfected cats were available for study. The prevalence of FIV was 14.6%. A single, FIV-uninfected cat was positive for FeLV antigen giving a prevalence of less than 0.2%.

Analysis of Risk Factors of FIV Infection

The mean age at testing was 9.8 (±4.3) years and 7.8 (±5.2) years for FIV-infected and uninfected groups, respectively. Mixed breed, male and neutered cats made up 88.2, 76.3, and 5.3% of the infected group in comparison to 66.2, 51.1, and 6.8%, respectively, of the uninfected group. The final multivariable model had three significant variables, "age at FIV testing", "sex", and "breed". The assumption of linearity for "age at FIV testing" was invalid, therefore, it was split into 4 categories: age ≤5 years, >5–10 years, >10–15 years, and >15 years. Results for the final model demonstrated that the risk of being FIV-infected was greater for cats over 5 years of age than for cats of 5 years of age or younger. Female cats (odds ratio [OR], 0.30; 95% CI, 0.17, 0.53) and purebred cats (OR, 0.28; 95% CI, 0.13, 0.56) were less likely to be FIV positive.

Analysis of Hematologic and Biochemical Data

Hematologic and biochemical results were analyzed for potential associations with FIV status. Of the 33 analytes evaluated, 9 had *P* values <.25 in univariable logistic regression analyses (Table 1). After adjusting for potential confounders, age and sex, only sodium was significant in the final logistic regression model. The assumption of linearity for sodium was not valid, therefore the cubic spline was fitted (data not shown). The results indicated that the log odds of being FIV-infected is increased as the sodium concentration increased above 150 mmol/L.

Comparison of Hematologic and Biochemical Parameters for FIV-Infected and FIV-Uninfected Cats with Normal Range for Each Analyte

Logistic regression analyses were conducted by categorizing all hematologic and biochemical parameters into three categories: decreased, normal, and increased. Of the 33 analytes evaluated, 11 were significant at a liberal *P*-value of .25 (Table 2). PCV, chloride, MCH, and MCHC were excluded from further analyses because of 0 or low frequencies for some cells. Only plasma sodium concentration and monocyte count were significant in the final model after adjusting for age and sex (Table 3). Compared with controls, the cases had greater odds of hypernatremia and decreased odds of hyponatremia. FIV-infected cats were at increased risk of monocytopenia (Table 3).

Hematologic and clinicopathological abnormalities that may be attributed to FIV infection, when it is present, are presented in Table 4. There was no significant difference in the frequency of these abnormalities between infected and control groups. Uninfected cats were as likely, or more likely, to be leukopenic, lymphopenic, hyperproteinemic, hyperglobulinemic, and azotemic than FIV-infected cats.

Table 1. Summary statistics of the association of hematological and biochemical parameters with FIV status.

Variable	Status	N	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	*P*-value
PCV (L/L)	FIV-infected	50	0.16	0.28	0.33	0.37	0.44	.052
	FIV-uninfected	162	0.05	0.25	0.31	0.36	0.46	
Hb (g/L)	FIV-infected	51	50.0	95.0	116.0	127.0	161.0	.057
	FIV-uninfected	167	6.6	89.0	107.0	124.0	160.0	
MCV (fl)	FIV-infected	50	37.1	43.3	46.05	49.7	60.2	.074
	FIV-uninfected	153	33.1	41.4	44.4	46.7	84.8	
MCH (pg)	FIV-infected	50	13.5	14.7	15.8	17.2	19.5	.006
	FIV-uninfected	160	1.6	14.05	15.2	16.3	24.2	
MCHC (g/L)	FIV-infected	50	312.0	335.0	343.0	353.0	400.0	.21
	FIV-uninfected	166	24.0	331.0	341.5	355.0	438.0	
Albumin (g/L)	FIV-infected	38	13.3	26.8	29.7	33.4	39.3	.022
	FIV-uninfected	131	7.43	29.3	32.5	34.7	43.0	
Cholesterol (mmol/L)	FIV-infected	36	1.8	2.8	3.4	4.5	137.0	.097
	FIV-uninfected	129	1.6	2.9	3.5	4.7	137.0	
CK (U/L)	FIV-infected	34	11.0	126.0	221.5	330.0	1323.0	.18
	FIV-uninfected	125	52.0	111.0	197.0	345.0	12726.0	
Sodium (mmol/L)	FIV-infected	35	132.4	146.4	151.5	155.8	162.1	<.001
	FIV-uninfected	130	126.4	139.7	144.6	148.7	172.6	

The *P*-values are for likelihood ratio chi-square test based on univariable logistic regression anlayses. Results are presented for only variables with *P*-value <.25.

Variables also examined but not significant ($P > .25$) were absolute erythrocyte reticulocyte, leukocyte, neutrophil (segmented and band), monocyte, eosinophil, basophil, lymphocyte and platelet counts, inorganic phosphate, glucose, creatinine, urea, total calcium, alanine aminotransferase, alkaline phosphatase, bilirubin, total protein, globulin, potassium, and chloride.

Table 2. Contingency tables of categorized hematologic and biochemical variables with FIV status.

Variables	Categories	FIV-infected (%)	FIV-uninfected (%)	Total	*P*-value
Sodium (mmol/L)	Decreased (≤147)	10 (28.6%)	81 (62.1%)	91	<.001
	Normal (>147–156)	18 (51.4%)	44 (33.9%)	62	
	Increased (>156)	7 (20%)	5(3.9%)	12	
Chloride (mmol/L)	Decreased (≤115)	7 (20%)	64 (50.8%)	71	.001
	Normal (>115–130)	28 (80%)	62 (48.4%)	90	
	Increased (>130)[a]	0 (0.0%)	2 (1.6)	0	
MCH (pg)	Decreased (≤13)[b]	0 (0.0%)	16 (10.0%)	16	.003
	Normal (>13–17)	36 (72.0%)	125 (78.1%)	161	
	Increased (>17)	14 (28.0%)	19 (11.9%)	33	
Monocytes × 10^9/L	Decreased (≤0.08)	8 (15.4%)	8 (5%)	16	.03
	Normal (>0.08–0.56)	33 (64.5%)	98 (61.3%)	131	
	Increased (>0.56)	11 (21.1%)	54 (33.8%)	65	
Bilirubin (μmol/L)	Decreased (≤2.5)	11 (57.9%)	37 (32.5%)	48	.11
	Normal (>2.5–3.5)	4 (21.1%)	35 (30.7%)	39	
	Increased (>3.5)	4 (21.1%)	42 (36.8%)	46	
Creatinine (μmol/L)	Decreased (≤90)	4 (9.5%)	24 (16.9%)	28	.17
	Normal (>90–180)	27 (64.3%)	97 (68.3%)	124	
	Increased (>180)	11 (26.2%)	21 (14.8%)	32	
Hb (g/L)	Decreased (≤80)	3 (5.9%)	27 (16.2%)	30	.11
	Normal (>80–140)	45 (88.2%)	128 (76.7%)	173	
	Increased (>140)	3 (5.9%)	12 (7.2%)	15	
MCV (fl)	Decreased (≤40))	6 (12%)	26 (17%)	32	.14
	Normal (>40–45)	15 (30%)	63 (41.2%)	78	
	Increased (>45)	29 (58%)	64 (41.8%)	93	
Calcium (mmol/L)	Decreased (≤1.75)	3 (7.3%)	2 (1.4%)	5	.18
	Normal (>1.75–2.6)	27 (65.9%)	101 (72.7%)	128	
	Increased (>2.6)	11 (26.8%)	36 (25.9%)	47	
PCV (L/L)	Decreased (≤0.30)	19 (38.0%)	80 (49.4%)	99	.15
	Normal (>0.30–0.45)	31 (62.0%)	81 (50.0%)	112	
	Increased (>0.45)[a]	0 (0.0%)	1 (0.6)	1	
MCHC (g/L)	Decreased (≤310)[b]	0 (0.0%)	8 (4.8%)	8	.18[b]
	Normal (>310–350)	37 (74%)	104 (62.7%)	141	
	Increased (>350)	13 (26%)	54 (32.5%)	67	

The *P*-values are for likelihood ratio chi-square test based on univariable logistic regression anlayses. Results are presented for only variables with *P*-value <.25.

[a]These categories were excluded from logistic regression analyses because of very small frequencies.

[b]The *P*-values are for Fisher's exact test as logistic regression model could not converge because of some zero cell frequencies.

Table 3. The final logistic regression model to evaluate association of categorized hematological and biochemical parameters with FIV status.

Variables	Categories	b	SE	Adjusted Odds Ratios	95% Confidence Intervals	*P*-value
Intercept		−3.50	0.91			
Sodium	Normal (>147–156)	0.00		1.00		.001
	Decreased (≤147)	−1.04	0.48	0.35	0.13, 0.89	
	Increased (>156)	1.89	0.83	6.63	1.41, 38.11	
Monocytes	Normal (>0.08–0.56)	0.00		1.00		.035
	Decreased (≤0.08)	1.96	0.81	7.13	1.50, 37.18	
	Increased (>0.56)	−0.14	0.51	0.87	0.31, 2.34	
Gender	Female	0.00		1.00		.017
	Male	1.24	0.52	3.44	1.31, 10.10	
Age at diagnosis	≤5 years	0.00		1.00		.053
	>5–10 years	1.60	0.86	4.95	1.08, 36.56	
	>10–15 years	2.25	0.85	9.51	2.16, 70.34	
	>15 years	1.14	0.99	3.14	0.49, 27.14	

Odds ratios are adjusted for other variables in the model. For example, compared to FIV uninfected cats, FIV infected cats had 6.63 times odds of having increased sodium concentrations and 7.13 times odds of decreased monocyte counts.

Table 4. Comparison of abnormalities commonly attributed to FIV infection in infected and uninfected cats.

	FIV-infected	FIV-uninfected
Abnormality	Affected/total (%)	Affected/total (%)
Leukopenia	21/52 (40.4)	66/161 (40.9)
Neutropenia	20/52 (38.5)	54/161 (33.5)
Lymphopenia	27/53 (50.9)	80/162 (49.4)
Hyperproteinemia	20/50 (40)	74/152 (48.7)
Hyperglobulinemia	8/37 (21.6)	30/129 (23.3)
Increased creatinine	4/42 (9.5)	24/142 (16.9)
Increased urea	7/43 (16.3)	33/145 (22.8)

There was no significant difference in these variables between FIV-infected and uninfected populations.

Table 5. The major clinical problem in FIV infected and uninfected cats.

Major clinical problem	FIV-infected (n = 75)		FIV/FeLV-uninfected (n = 230)		*P*
Cardiorespiratory	5	6.7%	18	7.8%	1.0
Endocrine	4	5.3%	15	6.5%	1.0
Gastrointestinal	10	13.3%	36	15.6%	.7
Genitourinary	4	5.3%	9	3.9%	.5
Healthy	4	5.3%	15	6.5%	1.0
Immune mediated	3	4.0%	12	5.2%	1.0
Infectious	10	13.3%	24	10.4%	.5
Neoplasia (total)	24	32.0%	55	23.8%	.2
lymphoid neoplasia	16	21.3%	30	13%	.1
Neurological	4	5.3%	20	8.6%	.5
No final diagnosis	7	9.3%	26	11.7%	.8

Comparison of Major Clinical Problem between FIV-Infected and Uninfected Cats

The major clinical problems identified in FIV-infected cats and the control sample are presented in Table 5. Almost 95% of all cats tested for FIV presented with clinical problems. In both groups, the most common clinical problems were neoplastic and gastrointestinal diseases and no significant differences between the groups were identified. Among cases of neoplasia, lymphoid malignancies were slightly more common in FIV-infected cats (16/75, 21.3%) than uninfected cats (30/230, 13%).

Comparison of Survival Time between FIV-Infected and Uninfected Deceased Cats

Thirty-eight FIV-infected and 134 uninfected cats died during the study period. Kaplan–Meier survival curves are shown in Figure 1. There was no difference in survival age ($P = .8$, log-rank test) or survival time ($P = .4$, log-rank test) between FIV-infected cats and uninfected cats.

Discussion

In this study, we combined analysis of hematologic and biochemical changes, major clinical problem and outcome in client-owned cats tested for FIV. FIV-infected cats were compared with an uninfected control group adjusted for age and sex. The prevalence of FIV in this group of predominantly sick cats was 14.6%, which is in accordance with previous studies of sick cats from the Asia Pacific region where FIV prevalence data are consistently among the highest found internationally.[21,22] In contrast, the finding of a single cat with FeLV antigenemia among 288 cats tested is consistent with the very low prevalence of FeLV in Australia.[23] Analysis of risk factors for FIV infection identified that mixed breed, male cats were more likely to be infected than purebred, female cats. Age also was a risk factor with older cats (>5 years old) being 4 times more likely to be FIV-infected than younger cats (≤5 years old). Similar risk factors have been reported worldwide demonstrating that our group displays characteristics typical for FIV-infected cat populations.[2,4,6,17]

A substantial proportion of FIV-infected cats was anemic (38%), lymphopenic (50.9%), or hyperproteinemic (40%). However, similar trends were observed in FIV-uninfected cats where 49.4% were anemic, 49.4% lymphopenic, and 48.7% hyperproteinemic. Multiple hematologic and biochemical abnormalities have been

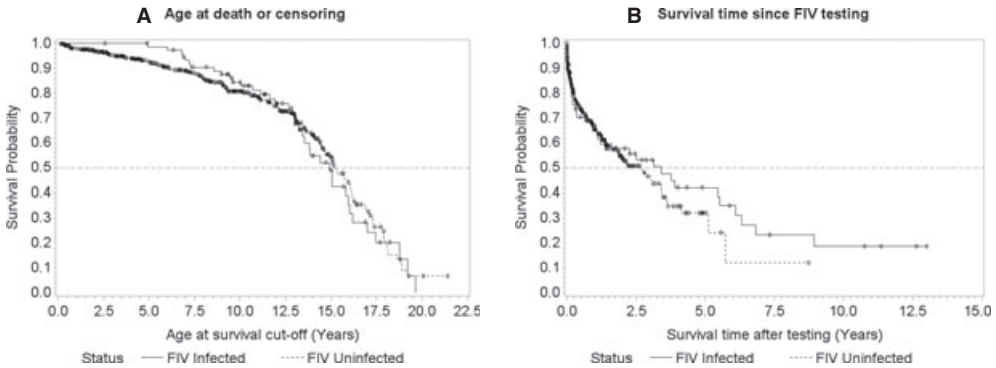

Fig 1. Kaplan–Meier curves showing survival of FIV-infected and FIV-uninfected cats. Curves for FIV-infected and uninfected groups indicate the proportion of surviving cats in each group at a given age (A) or after a given time after testing (B).

described as occurring commonly in FIV-infected cats, although matched, uninfected cats were not included in these early studies.[4,11,24–26] This highlights the importance of including a control sample when attempting to ascribe clinical relevance to such observations.

Significant differences in serum sodium concentrations were observed between infected and noninfected cats. The majority of controls were hyponatremic. Hyponatremia is the most common electrolyte disorder in sick humans and results from a diverse range of disease states and interventions.[27] These include liver disease, renal disease, vomiting, diarrhea, congestive heart failure, diuretic treatment, and hypotonic fluid administration.[28] FIV-infected cats were as likely to be hyponatremic as hypernatremic but, interestingly, infected cats were much less likely than controls to be hyponatremic. As the investigation of factors affecting sodium balance in individual cats was beyond the scope of this study, we can only speculate as to why there may be a decreased risk of hyponatremia in FIV infection. One explanation is a tendency for hypernatremia in infected cats that offsets hyponatremia seen in uninfected, sick cats. Significantly increased plasma sodium concentrations were reported in FIV-infected cats from 43 months postexperimental infection.[29] Among field cases, hypernatremia was present in 6% of 48 FIV-infected cats.[24] Hypotonic fluid losses through vomiting, diarrhea, fever, renal compromise, and decreased water intake can contribute to increased plasma sodium concentrations. Renal diseases are suspected in FIV infection, but a causal association has been difficult to prove.[30] We found no difference between FIV-infected cats and controls in plasma creatinine concentration, and genitourinary diseases were not a major problem in either group. Thirst could be decreased in FIV infection by a central effect, because some FIV isolates are neurotropic, or secondary to cognitive dysfunction, similar to AIDS dementia.[31,32]

An increased risk of hyperglobulinemia was reported in 2 controlled studies of natural FIV infection.[13,15] This likely reflects polyclonal B cell expansion, which is a hallmark of HIV infection in humans and has been documented in both natural and experimental FIV infection.[33,34] In experimentally infected cats followed longitudinally, plasma globulin concentration increased up to, but not after, 4.5 years postinfection.[29] It was postulated that this observation was because of the eventual onset of B cell loss. Advanced FIV infection is characterized by profound lymphoid depletion.[10,35,36] In a cross-sectional study of natural infection, Walker et al found lower proportions of B lymphocytes in cats with advanced disease compared with those at earlier stages.[37] In our study, hyperglobulinemia was seen in 21.6% of FIV-infected cats and in a similar proportion (23.3%) of uninfected cats. The mean age at diagnosis of FIV-infected cats was 9.8 years and it is possible that many had been infected for years, which might explain why no association with increased plasma globulin concentration was identified. Thomas and others reported a similar finding.[15] They demonstrated significant lymphopenia and hypergammaglobulinemia in cats naturally infected with FIV compared with controls, but when this relationship was analyzed in relation to age, it was found that neither variable was associated with FIV in cats >8 years of age.

FIV infection carried an increased risk of monocytopenia. Walker and Canfield also reported significant monocytopenia in FIV-infected pet cats compared with clinically matched, uninfected cats.[37] Bone marrow examinations of cats in this study identified a normal or proliferating myeloid pool. In cats with terminal illness, FIV sequences were found predominantly in cells of the monocyte/macrophage lineage raising the possibility of a direct viral effect on monocyte maturation as a cause of monocytopenia.[38]

Direct comparison between controlled field studies is hampered by differences in study populations, data collection, and analyses. Notwithstanding these differences in study populations and design, when data from controlled field studies, including ours, are considered as a whole no hematologic deficits have been consistently associated with FIV infection.[13–16,18,39] Thus, although retrovirus testing is indicated in the investigation of hematologic abnormalities, their presence in a sick, FIV-infected cat should not be interpreted as evidence that the prognosis for that cat is worse, compared with an uninfected cat with similar hematologic findings. For example, a number of abnormalities have been described in FIV-infected cats that could contribute to anemia, including decreased or aberrant erythroid maturation and hemostatic abnormalities.[18,25,40] However, anemia is a complex, multifactorial problem and its cause or causes may not always be identified in a sick cat with multiple problems. The fact that no other cause has been identified in an anemic patient infected with FIV does not imply that the problem is necessarily a consequence of FIV infection.

In 2 of 5 FIV-infected cats, the major clinical problem was lymphoid malignancy. Several lines of evidence support that, just as in HIV infection, there is a group of lymphoproliferative malignancies associated with FIV infection. An increased risk of developing lymphoma in natural FIV infection has been demonstrated.[41] Histopathological and immunohistochemical studies describe high-grade, B cell, extranodal neoplasms, features characteristic of HIV-associated lymphomas.[42] It will be important to further characterize malignancies arising in FIV-infected cats in the field to understand the spectrum of relationships between FIV and neoplasia and their etiologies.

The survival time was comparable between FIV-infected and uninfected cats. This contradicts a still widely held belief that FIV infection confers decreased life expectancy, but is in agreement with recent case control studies investigating similar numbers of FIV-infected pet cats as described in our study.[6,17] Similarly, survival in cats experimentally infected with FIV over a 6.5 year period (10/10) was comparable with that in uninfected controls (9/10).[29] In the largest study of almost 10,000 retrovirus tested pet cats, including 1100 seropositive for FIV, the survival rate at 6 years was

65% compared to 90% for uninfected cats.[43] Interestingly, if deaths during the first 100 days were excluded, survival of FIV-infected cats was 94 and 80% at 3 and 6 years, respectively, compared with controls. There is evidence that euthanasia based on the diagnosis of FIV infection may contribute to an observation of decreased survival in studies of FIV-infected cats. First, an investigation of risk factors for mortality in United Kingdom cat adoption centers found that, although FIV was the major single reason for euthanasia, no natural deaths could be attributed to this infection.[44] Second, Ravi and others reported that, of 58 FIV seropositive cats studied, 17 were euthanized at testing and in 9 of those the reason was the positive test result itself, rather than a specific clinical problem.[17]

The in-house testing kits used here perform well with sensitivities and specificities for FIV antibody detection approaching 100% when compared with western blot or with each other.[21,45] Confirmatory western blot testing was not performed but, as the results would be expected to vary little from serology, its value is questionable. The definitions of FIV-infected and FIV-uninfected used here combine history with results of serologic and, where indicated, molecular testing. This approach is necessary because of seroconversion following vaccination. Although it introduces potential errors in determining infection status, any such errors could have affected only a small proportion of cases reported here. The prevalence of FIV may have been higher than the 14.6% reported. Five cats that tested seropositive for FIV but with uncertain vaccination status, tested negative on PCR and were considered to be FIV-uninfected. This assumption may be false. It is not possible to eliminate the potential for vaccine-induced rather than infection-associated antibody in all cases. The sensitivity of PCR methodologies for detecting FIV is expected to be less than that of serology. The reported estimate of sensitivity of the PCR tests used here is similar, although lower, than estimates for serology.[19] Virus isolation after cocultivation of peripheral blood mononuclear cells is not practical to use as a confirmatory test because it is not commercially available and is not applicable to retrospective data sets. On the other hand, exclusion of another 5 seropositive cats of uncertain infection status may have falsely decreased the prevalence. A requirement for supportive evidence for defining FeLV antigen positive cats was imposed here because of the low prevalence of FeLV in this area and the subsequent poor positive predictive value of in-house tests.[23]

There are limitations to our study. The control population comprising cats 'at-risk' for FIV infection was selected because of its clinical relevance. These controls were crucial in identifiying the similarity of clinical abnormalities detected in cats tested for FIV, regardless of the outcome of the test. This control group is unlikely to be representative of the total population of FIV-uninfected cats. The quality of data from retrospective studies is limited by nonstandardized collection and incomplete data sets. The recording of the major clinical problem carries an element of subjectivity and does not account for the presence of multiple problems. The clinical consequences of FIV infection may be subtle and inconsistently detected at a population level, an issue that has hindered demonstration of pathogenicity of FIV strains infecting nondomestic species.[46] Many FIV-infected cats were censored from the survival analysis because they were still alive at the time of completion of the study and this should be noted when interpreting the data. Despite these drawbacks, studies of natural infection provide information relevant for practitioners faced with sick, FIV-infected cats.

Initial reports implying that FIV infection by itself imparts a poor prognosis should be interpreted with caution. Until surrogate markers for FIV disease progression are validated in longitudinal studies of naturally infected cats, the prognosis for an individual FIV-infected cat should be determined without regard to its FIV status.

Footnotes

[a] FIV, FeLV Rapid Immunomigration, AGEN Biomedical Ltd, Acacia Ridge, QLD, Australia
[b] Snap Combo, IDEXX Laboratories, Zetland, NSW, Australia
[c] Gribbles Veterinary Pathology, Clayton, VIC, Australia
[d] Vetpath Laboratory Services, Ascot, WA, Australia
[e] Fel-O-Vax FIV, Boehringer Ingelheim, Germany
[f] Microsoft Excel RAND function, 2007, Microsoft Corp, Redmond, WA
[g] SAS statistical software, release 9.3, 2002–10, SAS Institute Inc, Cary, NC

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