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Seroepidemiological and clinical survey of feline immunodeficiency virus infection in northern Italy

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Abstract

Four hundred and thirty-nine feline serum samples from cats with different living conditions in the north of Italy were tested for antibodies to feline immunodeficiency virus (FIV) and for antigen of Feline Leukemia Virus by enzyme-linked immunosorbent assay. A Western blot technique was also used on the positive sera in order to confirm the presence of specific antibodies to FIV. The Western blot enabled the detection of a false positive serum. The prevalence of FIV infection in this population was 12.5% and among the seropositive cats a greater proportion was male (74.5%) than female (25.5%). A correlation between the clinical status and the evolution of the pathology is described together with a score based on the severity of the stomatitis in infected cats. The Western blot patterns of positive samples were then compared with the stage of the pathology. Statistical analysis on the distribution of FIV in stray cats, cats with garden and courtyard access and strictly house-confined cats showed a highly significant risk of the infection in the first group.

Abbreviations

AC, asymptomatic carrier; BSA, bovine serum albumin; ELISA, enzyme-linked immunosorbent assay; FIV, feline immunodeficiency virus; HIV, human immunodeficiency virus; PGL, persistent generalized lymphoadenopathy; SDS, sodium dodecylsulfate; TBS, Tris-buffered saline.

Introduction

Feline immunodeficiency virus (FIV) is a lentivirus first isolated in 1986 from several cats exhibiting signs of immunodeficiency (Pedersen, 1987). Although phylogenetically FIV is closer to the ungulate lentivirus than those of the primates (Talbott et al., 1989), the clinical evolution of the pathology

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is in many ways very similar to the human immunodeficiency virus (HIV) infection in man. In addition, FIV shares many other features with HIV, e.g. the morphology, protein structure, reverse transcriptase enzyme and the tropism for T-lymphocytes.

However, FIV and HIV are antigenically dissimilar, insomuch that proteins of FIV are not recognized by antisera to HIV (Yamamoto et al., 1989). The relative molecular masses of the the envelope glycoproteins of FIV are 100/120 and 41 kDa, of the core proteins are 24, 14 and 10 kDa. The relative molecular mass of the reverse transcriptase is around 60 kDa (Pedersen, 1990). Other proteins of 14, 50 and 30 kDa may be detected as polyprotein precursors of the envelope, core and reverse transcriptase proteins, respectively (Pedersen, 1990).

In the cat, the infection is characterized by a transient primary illness lasting several weeks, followed by a long period of apparent normal health. Subsequently, clinical signs such as stomatitis, anorexia, diarrhea, weight loss, dermatitis and lymphoadenopathy may develop. Finally, FIV infected cats often die of opportunistic infection and/or tumors (Pedersen, 1990).

Following the experimental infection, the first antibodies to appear in the bloodstream are directed against 24, 41 and 50 kDa virion proteins; antibodies to the 10, 15 and 60 kDa come shortly after (Pedersen, 1990). Neutralizing antibodies to FIV appear rather early after the infection and are against the 100/120 kDa envelope glycoproteins (Gardner, 1991; Yamamoto et al., 1991).

This paper reports a serological survey of FIV infection, performed with an enzyme-linked immunosorbent assay (ELISA) technique and using Western blot to confirm the positivity. The clinical signs observed in the cats examined were related to the evolutionary phases of the pathology and a score based on the seriousness of the stomatitis in infected cats is presented. The Western blot patterns of positive samples have been compared with the stage of the pathology. All the data concerning the cats in the study were statistically evaluated by logistic regression.

Material and methods

Animals

The sera of four hundred and thirty-nine cats of different breeds, sex, age, origin and living conditions, submitted by practitioners in the north of Italy, were analyzed for FIV antibodies and FeLV antigens. The population analyzed consisted of 209 healthy cats and 230 cats with clinical signs resembling those of FIV infection. Detailed clinical histories and clinicopathological data of each cat were known. FIV-infected cats were grouped into five different stages: acute phase, asymptomatic carrier (AC), persistent generalized lym-

phoadenopathy (PGL), acquired immunodeficiency syndrome related complex (ARC) and clear AIDS according to their clinical signs (see Table 3). Moreover, a score based on the severity of the oral cavity lesions was produced (see Table 4).

Enzyme-linked immunosorbent assay test

A commercial ELISA test kit (Cite Combo, Idexx), detecting simultaneously the FeLV group specific antigen (p27) and antibodies to FIV in feline serum, was used for the screening. All the sera were then stored at −20°C for further analysis.

Western blot assay

Purified FIV, disintegrated with sodium dodecylsulfate (SDS)–mercaptoethanol sample buffer, was loaded on a 12% discontinuous SDS–polyacry-

Table 1
(a) Data of animals seropositive for FIV by ELISA

	Among seropositive cats		
	No. of FIV-positive (%)	No. of males (%)	No. of females (%)
Total	55 (12.5)	41 (74.5)	14 (25.5)
Description			
Entire	43 (78)	30 (73)	13 (93)
Neutered	12 (22)	11 (27)	1 (7)
Healthy	19 (35)	13 (32)	6 (43)
Sick	36 (65)	28 (68)	8 (57)
Breed			
Domestic	53 (96)	39 (95)	14 (100)
Siamese	1 (2)	1 (2.5)	0 (0)
Carthusian	1 (2)	1 (2.5)	0 (0)
Living conditions[a]			
S	19 (35)	12 (29)	7 (50)
H/S	26 (47)	23 (56)	3 (21)
H	10 (18)	6 (15)	4 (29)
Age (years) (mean age: 5.6 years)			
<1	4 (7)	1 (2)	3 (22)
From 1 to 5	22 (40)	20 (49)	2 (14)
From 6 to 10	11 (20)	9 (22)	2 (14)
From 11 to 15	6 (11)	4 (10)	2 (14)
>15	0 (0)	0 (0)	0 (0)
Unknown	12 (22)	7 (17)	5 (36)

[a]S, stray; H/S, house-kept, but with courtyard access; H, strictly house-confined.

Table 1
(b) Data of animals negative for FIV by serological tests (ELISA)

	Among seronegative cats		
	No. of cats seronegative for FIV and FeLV	No. of males	No. of females
Total	384	183	201
Description			
Entire	318	140	178
Neutered	66	43	23
Healthy	190	87	103
Sick	194	96	98
Breed			
Domestic	297	140	157
Purebreed	87	43	44
Living conditions[a]			
S	80	28	52
H/S	118	58	60
H	186	97	89
Age (years)			
<1	60	38	22
From 1 to 5	221	100	121
From 6 to 10	44	16	28
>10	28	15	13
Unknown	31	14	17

[a]S, stray; H/S, house-kept, but with courtyard access; H, strictly house-confined.

lamide gel (Laemmli, 1970). The separated proteins were transferred to nitrocellulose sheets which were cut into strips. Molecular weight (MW) standards were stained with Ponceau red and the remaining strips saturated with Tris-buffered saline (Tris 10 mM, NaCl 1.5 mM, pH 7.5) (TBS) solution containing 2.5% bovine serum albumin (BSA) blocking buffer. Each strip was incubated overnight at room temperature on a shaker with a 1:50 dilution of different sera in TBS–2.5% BSA. The strips were sequentially rinsed with TBS, TBS–0.05% Tween 20 and TBS and incubated for 90 min at room temperature on a shaker with goat anti-feline horseradish peroxidase conjugate diluted 1 : 1000 in TBS–2.5% BSA. After another rinse cycle the substrate (α-chloronaphthol) was added. Reactions were stopped with distilled water when visible bands had been established. The MW of FIV reactive peptides were determined by comparison with the standards of MW previously stained with Ponceau red.

Statistical analysis

Data were analyzed by logistic regression using the following model:

Table 2
Most frequent clinical signs in FIV-positive cats[a]

Description	No. of cases[b]	%
No. of positive cats with known anamnesis	55	
Oral cavity		
Stomatitis	16	29.6
Gastro-enteric tract		
Gastritis	2	3
Chronic enteritis	9	16
Other	1	1.8
Respiratory tract		
Tracheo-bronchitis	6	11
Pneumonia	3	5
Genito-urinary tract		
Cystitis	1	1.8
Nephropathy	7	12.5
Skin		
Mycosis	4	7
Infected fighting injuries	3	5
Non-mycotic alopecia	1	1.8
Other signs		
Weight loss	8	14.8
Hyperthermia	5	9
Otological disorders	5	9
Ocular disorders	6	11
Lymph node megalia	5	9
Neoplasms	2	3
Neurological signs	1	1.8

[a]Only one cat was also FeLV positive.
[b]Each cat showed more than one sign.

$$FIV = INT + BRD + SEX + REP + CLN + AGE + HOU$$

where FIV equals ELISA test, INT is intercept, BRD is breed, SEX is sex, REP is reproductive capability (entire or neutered), CLN is clinical symptoms, AGE is age, and HOU is living conditions.

Logistic regression is a model based on linear regression and it is one of the statistical techniques widely used in epidemiology (Hosmer and Lemeshow, 1989). Data were analyzed with procedure CATMOD of Statistical Analysis Systems (1987).

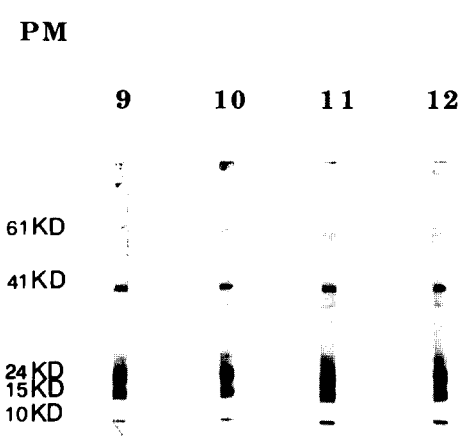

Fig. 1. Western blot patterns of ELISA FIV-positive cats. The numbers 9–12 correlate with the numbers 9–12 of ARC animals in Table 6. PM, relative molecular masses (kDa); SR, reference negative serum.

Results

This work surveyed 439 cats: 224 males and 215 females. Of those analyzed, 209 were healthy and 230 showed clinical symptoms. With regard to their living conditions 196 were strictly house confined, 144 were house kept but with courtyard access and 99 were strays. A significant fraction (12.5%) of cats was FIV seropositive using ELISA (Table 1(a)); 15.3% of cats presenting clinical illness were seropositive as opposed to 9.3% of the apparently healthy cats. In Tables 1(a) and 1(b) characteristics of ELISA seropositive and seronegative cats are shown. All cats in Table 1(b) were also seronegative for FeLV antigen. The peak of FIV infection appeared in cats between the ages of 1 and 5 years. The mean age of the FIV positive cats was 5.6 years.

Of FIV seropositive cats, 74.5% were males and 25.5% were females (Table 1(a)); 73% of the male positive cats were entire and 27% neutered, whilst 93% of the FIV infected female cats were sexually intact. Of the 99 stray cats examined, 19 (19%) showed antibodies to FIV. Cats kept in houses but with courtyard access had a similar prevalence (18%). On the contrary, only ten (5%) out of the 196 cats strictly house confined were FIV seropositive by ELISA.

A wide range of clinical signs was present in the sick cats that were proven to be FIV infected. The most frequent clinical signs were stomatitis, gastroenteric disorders, respiratory abnormalities, otological and ocular disorders and body weight loss as indicated in Table 2. A score based on the classification of oral cavity lesions of the seropositive cats is reported in Table 4.

The prevalence of the FeLV antigenemia in the tested animals was 2%. Forty-one out of 55 ELISA positive sera were still available for the Western

blot analysis. The specificity of the Western blot had been previously evaluated on sera from FIV infected cats and on sera of specific pathogen free (SPF) animals (data not shown). All but one of these sera showed specific antibodies to FIV polypeptides. In all the sera positive by Western blot, antibodies to p24 and p10 of FIV were always detected. In Fig. 1 some of the sera patterns analyzed with Western blot are visible. Attempts to correlate the Western blot patterns and the stage of the pathology were made. The serological status of the FIV positive cats tested in Western blot and their clinical stage are shown in Table 5.

The results of statistical analysis by logistic regression are shown in Table 6. The maximum likelihood analysis of variance (Table 6) shows that the proposed model fits (likelihood ratio, 92.31; $P=0.64$). The factors sex, age, living conditions and breed have a significant influence on the variance model, whilst clinical signs and the integrity of reproductive apparatus are not significant. However, these two latter factors have a positive contribution in the model fitting and so they were retained.

The risk estimates show that strays and males of domestic breed have the highest risk of being FIV positive, and the risk is three times higher during the first 5 years of life, while decreasing in older cats.

Discussion

In this report the prevalence of FIV infection in a large population of cats from the north of Italy is described. ELISA analysis showed that 12.5% of cats tested were seropositive for FIV. This rate is in agreement with other sero-epidemiological surveys performed worldwide (Ishida et al., 1989; Yamamoto et al., 1989; Lutz, 1990; Hosie et al., 1989). Among the cats with clinical illness a higher rate of FIV infection (15%) was detected. The consideration that some healthy cats (9%) were also seropositive to FIV is in accordance with what is known on the evolution of the disease. In fact, shortly after the viral infection a long period without clinical signs is typical of FIV disease (Pedersen, 1990).

In this regard attempts were made to follow the scheme of Ishida and Tomoda (1990) and Ishida et al. (1992) to classify the FIV infection into the five clinical stages of HIV infection, as shown in Table 3. The mean age of the seropositive cats classified in the AC group was 2.6 years while it was 5.8 years in the ARC group. This gap supports the hypothesis that a relatively long time lapse is required before the clinical signs develop. The division of the disease into stages represents a useful tool for the practitioner, since the survival time of a cat can be estimated and potential therapy against the opportunistic infections evaluated. In the field situation, it is relatively difficult to evaluate at which clinical stage a FIV positive cat can be classified, in particular regarding the acute phase, where there are no indications of when a cat

Table 3
Correlation between FIV positivity and clinical stage

Phases of disease	Symptoms	No. of FIV positive cats
Acute phase	Fever, lymphoadenopathy	4 (7%)
Asymptomatic carrier (AC)	No specific symptom	19 (35%)[a]
Persistent generalized lymphoadenopathy (PGL)	Lymph node megalia	4 (7%)
Acquired immunodeficiency syndrome (AIDS) related complex (ARC)	Loss of body weight, chronic enteritis, respiratory disease, stomatitis, skin lesions, lymphoadenopathy	24 (44%)[a]
Clear AIDS	ARC plus opportunistic infections and/or tumors	4 (7%)

[a]One of these cats was also FeLV positive.

became infected (Lutz et al., 1988). In this work it has been possible to determine this data by performing the screening test on previously healthy cats that showed a sudden illness. Many of these cats had been regularly taken to the practitioner and thus had a known remote anamnesis. Furthermore, in subsequent visits the same cats were shown to have recovered completely. Hence it was possible to be certain that the cats were in the acute phase of the infection when screened.

When examining the clinical signs of each FIV seropositive cat (Table 2), stomatitis was the most frequently noted symptom. This result is in accordance with previous findings, although not every cat with mouth disease is FIV infected (Pedersen, 1990). Other authors (Kolbl and Lutz, 1992) correlate stomatitis with spumavirus infection. The score based on the oral cavity lesions that is proposed in this work facilitates the identification of the severity of the stomatitis (Table 4). By using this score it would be easier to collect the data during the clinical examination thus facilitating the subsequent analyses. In this survey it was observed that only 9% of cats with FIV infection showed fever. This is in contrast with the findings of Lutz et al. (1990). Since many of the cats analyzed were visited by practitioners who referred the clinical status to the authors, it is possible that in some of the cats the temperature had not been taken. This could explain the relatively small percentage found.

Western blot has proved to be a highly sensitive technique in the detection of antibodies to FIV, enabling an ELISA false positive serum to be ruled out. In the early phases of the disease antibodies to p10 and p24 were always detected, suggesting that they are most likely the first antibodies to appear, while in other cats of the same stage antibodies to other viral polypeptides (p10, p15, p24, gp41, p60 and/or p30) of FIV can be recognized. As the disease

Table 4
Classification of the oral cavity lesions in FIV-positive cats

	Score based on the oral cavity lesions				
	0[a]	1[b]	2[c]	3[d]	4[e]
No. of observed cases	39	4	3	4	5

[a]Normal, healthy gingiva.
[b]Gingival blushing.
[c]Heavier blushing, gingival exudation and proliferation.
[d]Heavier blushing, gingival exudation and proliferation, gingival ulcera, gingival detachment and formation of gingival pockets.
[e]Heavier blushing, gingival exudation and proliferation, gingival ulcera, gingival detachment and formation of gingival pockets, tongue ulcera and palate lesions.

progresses the cats show an increased immunoreactivity detectable by additional bands in Western blot analysis.

In the light of these considerations it is most likely that cats in the AC or PGL phases showing a similar Western blot pattern have been infected for a long time and are on the borderline of ARC. These data were partially confirmed by the follow-up of two animals that were classified in the AC phase but had a Western blot pattern for ARC. They were clinically examined after 5 months and they were beginning to show symptoms of the ARC phase confirming the findings of Ishida et al. (1992). It is therefore stated that the estimation of the Western blot pattern could be of some help to the practitioner, although never replacing a clinical examination in evaluating the prognosis of the patient.

The analysis of the risk estimates by logistic regression showed some interesting findings. Domestic breeds have a higher risk than purebreeds of being positive to FIV. Whether the purebreeds have a genetic resistance to the FIV infection is, however, difficult to evaluate; besides, purebreeds are probably looked after better, which may influence the prevalence of FIV. Another survey taking into account a larger number of purebreeds could confirm an eventual genetic resistance. Male cats have a risk four times higher (Table 6) than female, but it is independent from the integrity of reproductive apparatus. Moreover, the absence of risk in house-kept cats with courtyard access seems to prove that the sexual transmission should be negligible. The highest risk of being positive is in the stray cats, but in this case the probability of being infected is easily explained. Agressivity, territorial defence and fighting over females are very common habits in the life of stray cats. Considering the most likely natural transmission of FIV among cats through bites involving infected saliva (Yamamoto et al., 1988; Pedersen, 1990), the higher level of infection in these groups was as anticipated. In the whole cat population examined it was observed that 19% of stray cats were FIV seropositive, as op-

Table 5
Correlation between Western blot patterns and the stage of FIV infection

Phase of disease	Animals tested in Western blot	p24	p10	p15	gp41	p60	p30
Acute phase	1	*	*			*	
Asympt. carrier	1	*	*			*	
	2	*	*			*	
	3	*	*				
	4	*	*				
	5	*	*	*	*		
	6	*	*	*	*		
	7	*	*	*	*	*	
	8	*	*	*	*		*
	9	*	*	*	*	*	
	10	*	*	*	*	*	
PGL[a]	1	*	*			*	
	2	*	*				
	3	*	*	*	*	*	
ARC[b]	1	*	*	*	*	*	
	2	*	*	*	*	*	
	3	*	*	*	*	*	
	4	*	*	*	*	*	
	5	*	*	*	*	*	
	6	*	*	*	*	*	
	7	*	*	*	*	*	*
	8	*	*	*	*	*	
	9	*	*	*	*	*	
	10	*	*	*	*	*	
	11	*	*	*	*	*	
	12	*	*	*	*	*	
	13	*	*	*	*	*	
	14	*	*	*	*	*	*
	15	*	*	*	*	*	
	16	*	*	*	*		*
	17	*	*	*	*		*
	18	*	*	*	*	*	
	19	*	*	*	*	*	
	20	*	*	*	*	*	
	21	*	*	*	*	*	
	22	*	*	*	*	*	
	23	*	*	*	*	*	
Clear AIDS	1	*	*	*	*	*	
	2	*	*	*	*	*	

[a]Persistent generalized lymphoadenopathy.
[b]AIDS related complex.

posed to 5% of house-confined cats. It is interesting to notice that, even if the disease has a long incubation period, in this survey, by far the highest risk of infection is in the first 5 years of life, while after this period the risk of being

Table 6
Logistic regression: analysis of variance and risk estimates

Factors	Levels	Risk estimates	*P* level	*P* factor
Sex	Male	3.74	0.0002	0.0002
	Female	1.00		
Reproduction	Entire	0.92	0.8447	0.8447
	Neutered	1.00		
Age	1–5 years	3.07	0.0306	0.0137
	6–10 years	0.51	0.0595	
	11–15 years	0.65	0.6258	
	> 15 years	0.39	0.1867	
	< 1 year	1.00		
Living conditions[a]	S	5.27	0.0021	0.0089
	H/S	0.49	0.1026	
	H	1.00		
Breed	Domestic	4.52	0.0485	0.0485
	Purebreed	1.00		
Clinical symptoms	Healthy	1.24	0.5278	0.5278
	Sick	1.00		

Likelihood ratio, 92.31; df 98; $P=0.643$.
[a]S, stray; H/S, house-kept, but with courtyard access; H, strictly house-confined.

infected is very low.

There is a striking similarity between FIV and HIV, since also in the feline AIDS a very important role is played by the risk of exposure of the cat to FIV, allowing the identification of category of cats at more risk of infection. Since FIV, along with all the other members of the lentivirus genus, has a very low survival rate outside the organism (Narayan, 1990), transmission is therefore the Achilles' heel in the biology of lentiviruses. Retrospective surveys on FIV have enabled the indentification of seropositive sera as far back as stored sera are available (Gruffyd-Jones et al., 1988; Sabine et al., 1988; Shelton et al., 1990), suggesting that FIV has existed in the cat population for hundreds of years (Pedersen, 1990).

In the last several decades there has been a large rise in the number of household pets and stray pets including cats. This has resulted in increased number of catteries or multiple-cat households where intimate contact among cats of different origin provides a mechanism for the transmission of contaminated viral fluids.

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