Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

J. Comp. Path. 1992 Vol. 107, 411–425

Feline Non-suppurative Meningoencephalomyelitis. A Clinical and Pathological Study

A.-L. Lundgren

Department of Pathology, Faculty of Veterinary Medicine, Swedish University of Agricultural Sciences, Uppsala, Sweden

Summary

A spontaneous neurological disease in cats characterized by behavioural and motor disturbances was investigated by clinical, morphological and immunological methods. Neuropathological examination showed a marked inflammatory reaction in the cerebral leptomeninges and the grey matter of the brain. In the white matter, the reaction was moderate. The changes consisted of perivascular cuffing by mononuclear cells and neuronal damage. The brain stem (thalamus, mesencephalon, caudal colliculus) was most severely affected. The spinal cord and its leptomeninges were involved to a lesser degree. The histopathological picture as well as the laboratory findings suggests a viral cause of the disease. The morphology of the disease and serological as well as immunohistochemical results indicate that this disorder is different from previously known feline viral encephalitides.

Introduction

Feline non-suppurative meningoencephalomyelitis comprises a group of diseases which apparently are related. The syndrome seems to be geographically widespread since cases have been reported from Australia (Borland and McDonald, 1965), the United States (Vandevelde and Braund, 1979) and Switzerland (Hoff and Vandevelde, 1981). Suspected cases have also been recorded in Morocco (Martin and Hintermann, 1952) and Sri Lanka (McGaughey, 1953). A similar clinical condition affects lions, tigers and other large cats (Flir, 1973; Melchior, 1973; Gutter, Wells and Baskin, 1983; Truyen, Stockhofe-Zurwieden, Kaaden and Pohlenz, 1990).

In 1974, Kronevi, Nordström, Moreno and Nilsson reported the occurrence in Sweden of a feline neurological disorder with the histological features of a non-suppurative meningoencephalomyelitis. Thirty cats were affected, seven of which were examined post mortem. These showed, throughout the brain and spinal cord, mononuclear perivascular cuffing, gliosis and meningitis. The lesions were most pronounced in the brain stem. The authors thought the disease was a specific entity, but did not express an opinion as to its aetiology. Serological screening for viral agents was not performed by Kronevi *et al.* (1974) and efforts to isolate a virus yielded negative results.

Address for correspondence: Anna-Lena Lundgren, Department of Pathology, Swedish University of Agricultural Sciences, P.O. Box 7028, S-750 07 Uppsala, Sweden.

0021-9975/92/080411 + 15 $08.00/0

Since the report by Kronevi *et al.* (1974), the disease has become recognized in certain parts of Sweden and is referred to as "staggering disease". In 1992, Ström reviewed the clinical findings in 33 cases of staggering disease recorded from 1988 till 1990. The author performed serological screening for feline leukaemia virus (FeLV), feline immunodeficiency virus (FIV), feline coronavirus (FCoV), *Toxoplasma gondii* and *Borrelia burgdorferi* in some of the diseased cats. The results were negative with the exception of one cat, which was positive for antibodies to FIV.

There have been doubts as to whether staggering disease is a specific entity. It has been argued that the syndrome may include several aetiologically unrelated conditions affecting the central nervous system of cats, e.g. toxoplasmosis (Hirth and Nielsen, 1969) and the cerebral form of feline infectious peritonitis (Slauson and Finn, 1972; Kornegay, 1978). In order to establish whether staggering disease is a specific entity, it was decided to perform a systematic and thorough neuropathological examination of a larger number of cats than were included in the original report by Kronevi *et al.* (1974). Furthermore, it was decided to discuss the possible aetiology of the disease based on modern knowledge of feline infectious agents. The present investigation details the pathological and clinical features of staggering disease and includes a search for aetiological agents with the use of immunohistochemistry and serology.

Materials and Methods

Animals

From January 1990 till March 1992 a total of 316 cats was referred to the Department of Pathology, Faculty of Veterinary Medicine, Uppsala, for post mortem examination. Sixty-three of the cats were diagnosed as having staggering disease. From this group, 25 cases that were clinically well documented were chosen for the present investigation.

Clinical examination and treatment of most of the cats took place at the University Clinics, Faculty of Veterinary Medicine, Uppsala. The author performed clinical examination of six cats as well as interviews with their owners. Fifteen cats were examined by several small animal veterinarians at the University Clinics. Four cats were clinically examined at private veterinary clinics and afterwards referred to the Department of Pathology for necropsy. One cat died of the disease. The others were killed by pentobarbital overdose. All cats with staggering disease were investigated post mortem by the author.

Morphology

Tissue specimens were fixed in buffered 10 per cent formalin for light microscopy. The brain and spinal cord were removed from all cats for examination. Coronal sections of the brain included the frontal, parietal, temporal and occipital lobes, basal ganglia, hippocampus, thalamus, mesencephalon, caudal colliculus, cerebellum and obex. From the spinal cord, sections were taken from cervical, thoracic and lumbar segments. The number of cases in which the different parts of the brain and spinal cord were examined are shown in Table 3.

In 12 cases, portions of the proximal sciatic nerve were taken for histological examination. Portions of the eyes and sartorius muscles were taken from eight cats. The cranial mesenteric ganglion was examined in four cases. Samples were removed from the liver in 25, the kidney, heart and spleen in 24, the lung, mandibular gland and

small intestine (jejunum) in 22, the pancreas in 20 and the retropharyngeal lymph nodes in five cats.

Paraffin wax sections were cut 4 μm thick and stained with haematoxylin and eosin (HE). Sections of the basal ganglia, hippocampus, thalamus, mesencephalon, caudal colliculus, obex and the spinal cord were stained with Luxol fast blue, Nissl, Giemsa, phosphotungstic acid haematoxylin, Gomori's reticulin and Lendrum's stain for inclusion bodies in selected cases.

Scoring of Light Microscopic Changes

To estimate the inflammatory changes, the presence of perivascular cuffs and inflammatory nodules consisting of lymphoid cells and macrophages (as described by Leestma, 1991) was recorded in each examined section of the central nervous system (Table 3). Perivascular cuffs were counted in at least 5 low power fields (LPF) with a diameter of 5 mm and rated + = 1 to 3/LPF, + + = 4 to 6/LPF, + + + = > 6/LPF. The thickness of the perivascular cuffs was rated from 1 to 4 where 1 = one cell thick, 2 = 2 to 3 cells, 3 = 4 to 6 cells, 4 = more than 6 cells. The size of the inflammatory nodules was rated from 1 to 3 where 1 = a few cells, 2 = moderate cluster of cells, 3 = extensive cellular infiltration. The presence of inflammation in the leptomeninges was graded from 1 to 3 with regard to the degree of cellular infiltration where 1 = slight, 2 = moderate, 3 = severe.

Immunohistochemistry

In five cats, material from the parietal lobe, basal ganglia, thalamus, mesencephalon, caudal colliculus, cerebellum and pons were fixed in buffered 10 per cent formalin for 48 h and then examined for the presence of pseudorabies virus antigen, canine distemper virus (CDV) antigen and *Toxoplasma gondii* antigen, by the peroxidase-antiperoxidase (PAP) immunohistochemical method (Sternberger, 1979) with polyclonal primary rabbit antibodies kindly supplied by P. De Groot, Rijksuniversiteit, Ghent, Belgium (pseudorabies), C. Örvell, Swedish National Bacteriological Laboratory (CDV) and A. Uggla, Swedish National Veterinary Institute (*Toxoplasma gondii*).

Blood Chemistry and CSF Analysis

Complete blood analysis was performed in 11 cats. The tests included haemoglobin concentration, total white blood cell count (WBC) and differential cell count, packed cell volume (PCV) and alanine aminotransferase and urea concentrations. In three other cats, only haemoglobin concentration and WBC were analysed.

Cerebrospinal fluid (CSF) of seven cats was obtained by cisternal puncture and examined for colour, turbidity, protein content, total red (RBC) and white blood cell (WBC) counts and differential cell count.

Serology

Serum from 11 cats was tested for the presence of FeLV antigen and antibodies to FIV using an enzyme-linked immunosorbent assay (ELISA) kit (CITE-COMBO-Test, IDEXX Corp., Portland, ME, U.S.A.). Serum was tested for antibodies to FCoV in nine cats with an ELISA kit supplied by SVANOVA Biotech, Uppsala, Sweden. In seven cats, serum was tested for antibodies to *Borrelia burgdorferi* with an indirect immunofluorescent antibody (IFA) test (Burgess, 1986) with a human *Borrelia burgdorferi* isolate as antigen. In five cats, serum was tested for antibodies to tick-borne encephalitis virus (TBEV) by the haemagglutination inhibition (HI) method with 1-day-old chicken erythrocytes starting with serum diluted 1 in 10 (Kunz, Hofmann and Dippe, 1971).

Results

History and Clinical Observations

Some of the cats with staggering disease came from urban, but mostly (68 per cent) from rural surroundings of Uppland and Mälardalen, Sweden. Cases of the disease occurred throughout the year, but most often from December to May.

The cats were aged 1 to 12 years, the mean age being 4·8 years. Fifteen cats were male (60 per cent), twelve of them neutered. Twenty-one cats (84 per cent) were short or long haired domestic cats, two were Siamese, one Abyssinian and one a Norwegian Forest cat. Twenty cats (80 per cent) were allowed to roam freely outdoors.

One cat came from a home where two other cats previously had been affected by staggering disease. Four cats came from households where there were other cats unaffected by the disease. One cat had experienced several upper respiratory tract infections during a period of 9 months before showing signs of staggering disease. Three to 6 months before showing the first signs of staggering disease, eight cats (32 per cent) were infested with ticks.

The vaccination status of most cats was unknown; six had been vaccinated against feline panleukopenia.

The most striking clinical manifestations (Table 1) were a stiff staggering gait, inability to jump up and down normally and inco-ordination of the hindlegs followed by weakness and paresis. Some cats lost their ability to retract their claws. In addition to these motor disturbances, many cats showed mental changes. Cats previously shy became social and affectionate, mewing more than usual, while cats that were customarily cheerful and affectionate became introverted and shy. Aggressive behaviour was rare. Depression, loss of appetite and dehydration were seen in many cases.

Less frequent signs included pruritus, hypersensitivity to sound and light, increased salivation, impaired vision, staring gaze, hyperaesthesia, constipa-

Table 1
Major clinical findings in 25 cases of feline non-suppurative meningoencephalomyelitis

	Per cent
Hindleg ataxia	84·0
Fever	47·4
Depression	44·0
Reduced appetite	40·0
Lumbosacral pain	36·0
Dehydration	32·0
Inability to retract the claws	32·0
Mewing more than usual	32·0
Increased affection	28·0
Pruritus	16·0
Hypersensitivity to sound and light	12·0
Increased salivation	12·0

tion, tremor, circling and seizures. The rectal temperature was measured in 19 cats. Nine of these (47·4 per cent) were febrile (> 39·5°C). In the final stages of the disease the hindlegs were paralysed. All cats remained conscious to the end.

Most cats were treated with antimicrobial drugs such as tetracycline, ampicillin and chloramphenicol. Intravenous fluids and B-vitamins were administered in many cases. Some cats were given corticosteroids. Despite treatment, the condition of the cats deteriorated and most cats had to be killed after 1 to 4 weeks illness. Two cats were severely ill from the onset of the disease and had to be put down in less than a week. A few cats recovered incompletely. The only cat who died naturally of the disease did so after 4 weeks.

Laboratory Findings

A moderate leukopenia (2·6 to 4·1 × 10^9 cells per l) was found in five of 14 cats examined. In two of the cats with leukopenia, the differential cell count was normal. The other three cats with leukopenia showed mild neutropenia and mild lymphocytosis; the neutrophil-lymphocyte ratio being 32:58, 32:59 and 33:66, respectively (normal range of the neutrophil count: 35 to 75 per cent; normal range of the lymphocyte count: 20 to 55 per cent). One cat in the final stage of the disease exhibited a WBC count of 15·4 × 10^9 cells per l and a neutrophil-lymphocyte ratio of 93:1.

Haemoglobin concentration (normal value 80 to 150 g per l) and PCV (normal value 24 to 45 per cent) were normal except for slightly raised values in dehydrated animals. Alanine aminotransferase (normal value < 1·2 μkat per l) was moderately raised in four cats ($n = 12$). Urea concentration ($n = 11$) was normal (4·5 to 13·0 mmol per l) in 10 cats and slightly raised in one cat (14·0 mmol per l).

Cerebrospinal fluid (Table 2) was transparent and colourless in all cases, showed a moderate elevation in protein content (normal value < 25 mg per dl) in six cats and an increased WBC count (normal value < 5 cells per μl) in four cats.

All sera examined for antibodies against FIV and presence of FeLV antigen were negative. Six of the cats tested for antibodies against FCoV were negative (titre < 1 in 10). In two cats the FCoV antibody titre was 1 in 10 and 1 in 320, respectively. All sera examined for antibodies against *Borrelia burgdorferi* and TBEV were negative.

Pathology

Central Nervous System. One cat that had been ill for 10 months exhibited a slight thickening and opacity of the cerebral leptomeninges. In the other cases, the brain and spinal cord did not show any abnormal changes on naked eye inspection.

Histopathological examination revealed throughout the central nervous system a non-suppurative inflammation characterized by perivascular mononuclear cuffing, presence of inflammatory nodules and neuronal degeneration in all cats. Perivascular cuffs occurred within Virchow-Robin spaces and

Table 2
Cerebrospinal fluid (CSF) analysis in seven cats with non-suppurative meningoencephalomyelitis

Case no.	*Breed*	*Age (years)*	*Sex*	*Duration of illness*	*CSF colour*	*CSF character*	*Protein content mg per dl*	*RBC cells per µl*	*WBC cells per µl*	*Diff. count: mononuclear leucocytes per cent*	*Diff. count: polymorphonuclear leucocytes per cent*
276/91	Siamese	4	F	4 weeks	Colourless	Transparent	70	2450	50*	100	0
463/91	DLH	9	NM	3 days	Colourless	Transparent	60	0	5	20	80
473/91	DSH	3	F	4 weeks	Colourless	Transparent	56	9400	2	100	0
92/92	DSH	8	F	10 months	Colourless	Transparent	30	0	0	ND	ND
154/92	DLH	8	NM	6 weeks	Colourless	Transparent	40	9	8	100	0
166/92	DSH	12	NF	3 weeks	Colourless	Transparent	68	0	12	100	0
249/92	Abyssinian	5	NF	4 weeks	Colourless	Transparent	< 11	0	12	83·3	16·7

Abbreviations: F = female, NF = neutered female, M = male, NM = neutered male, DSH = domestic shorthair, DLH = domestic longhair, RBC = red blood cells, WBC = white blood cells, ND = not done.
* After correction for blood contamination (Fenner, 1989), the WBC count in case 276/91 is approximately 46 cells per µl.
Normal CSF values: protein content < 25 mg per dl, WBC < 5 cells per µl.

around small vessels (Fig. 1). The cell population of the cuffs consisted of lymphoid cells, histiocytes, occasional plasma cells and macrophages laden with lipid-like material. The cuffs were one to six cells thick and sometimes seemed to compress the lumen of the vessels. The endothelial cells were swollen, but vascular thrombosis and vasculitis were not seen. Neurones adjacent to cuffed vessels sometimes appeared shrunken and uniformly acidophilic. Perivascular cuffing was less prevalent and less severe in the white matter than in the grey matter.

Inflammatory nodules consisting of aggregates of lymphoid cells and macrophages, as described by Leestma (1991), were frequently seen in the grey matter. Neuronal degeneration and neuronophagia (Fig. 2) occurred in all parts of the CNS except for the cerebellum. Inclusion bodies were not identified. Some large neurones, such as the hypoglossal nerve cells, contained small, cytoplasmic, eosinophilic granules. These were not further characterized.

Meningitis was present over all parts of the brain, but was most prevalent over the cerebral cortex and cerebellum (Fig. 3). Spinal cord meningitis was slight and sometimes absent. The meningeal inflammatory cells were of the

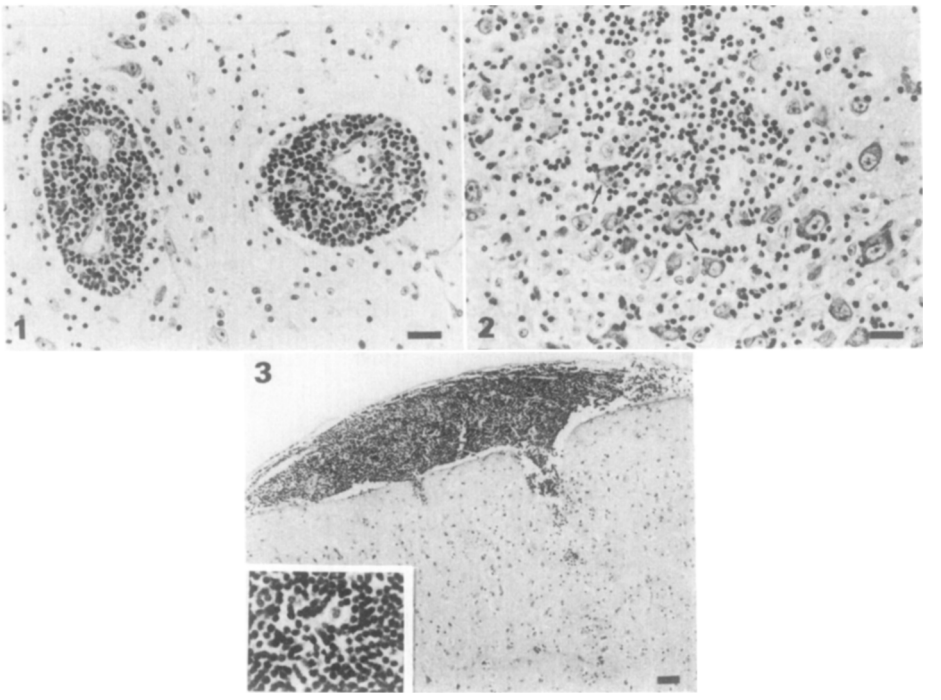

Fig. 1. Caudal colliculus, case 35/91. Perivascular cuffing by lymphoid cells and histiocytes. Giemsa. Bar = 20 μm.

Fig. 2. Hippocampus, case 113/91. Neuronophagia (arrows) and inflammatory infiltrate consisting of lymphoid cells and macrophages. Giemsa. Bar = 20 μm.

Fig. 3. Parietal cortex, case 2/92. Inflammatory infiltrate, mainly consisting of lymphoid cells (inset, × 360), in cerebral leptomeninges. HE. Bar = 50 μm.

same type as in the cuffs. In the cat that had been ill for 10 months there was a moderate fibrosis of the cerebral leptomeninges.

On the basis of classification and scoring of lesions, a localization pattern emerged (Table 3; Fig. 4). The most severe inflammatory changes were seen in the grey matter of the brain stem (thalamus, mesencephalon, caudal colliculus), basal ganglia and hippocampus. Moderate inflammation was observed in the cerebral cortex. Parenchymal lesions in the cerebellum were slight or absent, whereas cerebellar meningitis was severe. In the medulla oblongata, lesions were not as extensive as in the more proximal sections of the brain stem. At all levels of the spinal cord, inflammatory changes were moderate and mostly confined to grey matter. The lesions occurred in the ventral and dorsal horns with no apparent predilection for either place. Degeneration of myelin was sometimes observed in the spinal ventrolateral tracts. The spinal nerve roots did not show any abnormalities.

Table 3
Frequency (per cent of number of cases) of perivascular cuffing (P), inflammatory nodules (I), neuronophagia (Ne) and meningitis (M) in various parts of the central nervous system in feline non-suppurative meningoencephalomyelitis

	P		*I*		*Ne*	*M*
Part of CNS	*Grey matter per cent*	*White matter per cent*	*Grey matter per cent*	*White matter per cent*	*Per cent*	*Per cent*
Frontal lobe $n=25$	96·0	68·0	28·0	4·0	24·0	76·0
Parietal lobe $n=25$	92·0	56·0	12·0	4·0	12·0	84·0
Temporal lobe $n=25$	88·0	68·0	16·0	4·0	16·0	68·0
Occipital lobe $n=24$	91·7	70·8	12·5	0	4·2	70·8
Hippocampus $n=20$	95·0	25·0	40·0	5·0	35·0	70·0
Basal ganglia $n=23$	100	52·2	43·5	4·4	34·8	60·9
Thalamus $n=25$	100	44·0	60·0	0	52·0	44·0
Mesencephalon $n=23$	100	21·7	60·9	4·4	34·8	69·6
Caudal colliculus $n=24$	100	33·3	62·5	0	33·3	45·8
Obex $n=25$	100	36·0	40·0	0	16·0	28·0
Cerebellum $n=25$	28·0	36·0	4·0	0	0	92·0
Cervical spinal cord $n=23$	95·7	47·8	30·4	0	13·0	26·1
Thoracic spinal cord $n=23$	87·0	30·4	21·7	0	4·4	13·0
Lumbar spinal cord $n=22$	90·9	45·5	18·2	0	9·1	22·7

n = Number of cases examined.

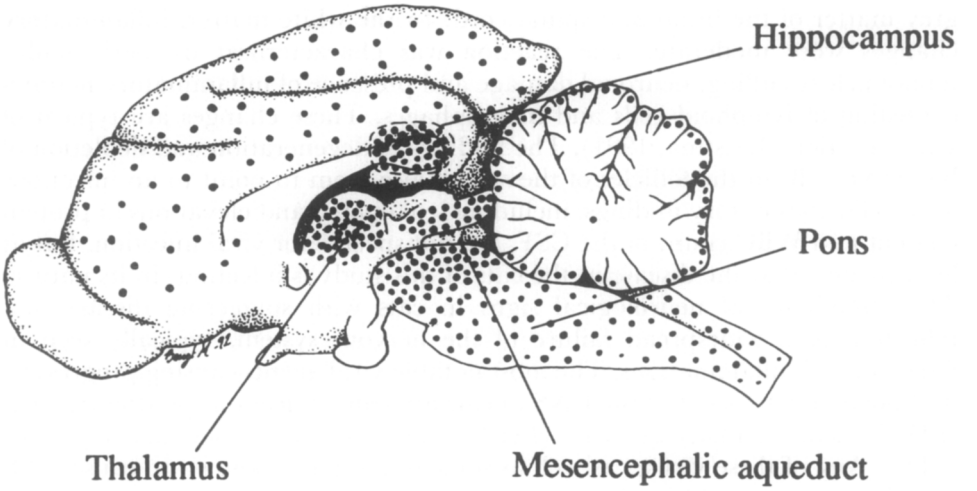

Fig. 4. Localization pattern and intensity of lesions in various parts of the brain in feline non-suppurative meningoencephalomyelitis. Drawing: Bengt Matsson.

Immunohistochemical examination by the PAP method for the antigens of pseudorabies virus, CDV and *Toxoplasma gondii* yielded negative results. Positive control sections were stained and examined in all cases.

Other Tissues. Five cats were in poor physical condition. The urinary bladder of two cats was severely distended with urine. Marked constipation of the rectum was evident in four cats. One cat had multiple small cysts in the cortex of the kidneys. Other gross lesions were not observed.

The liver of three cats showed varying degrees of fatty change. The cortex of the kidney of 12 cats exhibited small interstitial collections of lymphocytes, histiocytes and plasma cells.

The retropharyngeal lymph nodes showed follicular hyperplasia and abundant accumulation of lymphocytes in cortex and paracortex in five cats. In eight cats, the lymph follicles of the spleen were reduced in number. The germinal centres, although large in size, were markedly lacking cells and in some cases showed degenerative changes of the central area (karyorrhexis, karyolysis and formation of an amorphous eosinophilic material). Depletion of lymphoid cells was evident in the marginal zones of the follicles and in the periarteriolar lymphatic sheath (T cell area).

Small perivascular lymphocytic accumulations were seen in the cranial mesenteric ganglion of two cats ($n=4$). The eyes and skeletal muscle showed no pathological changes. There were no abnormalities in the sciatic nerve of any of the cats examined.

Discussion

Neuropathological examination of the cats of the present study showed a marked inflammatory reaction in the cerebral leptomeninges as well as in the

grey matter of the brain and spinal cord. In the white matter, inflammatory changes were moderate. The reaction was characterized by perivascular mononuclear cuffing, neuronal damage and presence of inflammatory nodules consisting of lymphoid cells and macrophages. These changes are typical of viral infection (Leestma, 1991). The findings of degeneration and depletion of lymphoid cells in the follicles of the spleen also seem to point to an infectious agent. The laboratory findings, including leukopenia and elevations in protein content and WBC count of the CSF, are not specific for viral infection, but at least suggest that the disease in the cats of this study is infectious in its nature. The abundance of neurological signs in cats with staggering disease is a reflection of a widespread failure of the nervous system, typically seen in disseminated inflammations. The most notable viral agents causing progressive multifocal involvement of the CNS in cats are feline infectious peritonitis virus (FIPV), feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV). Any of these viruses as well as some other agents known to cause CNS disorders in cats could be the cause of staggering disease.

The central nervous system form of feline infectious peritonitis (FIP) is manifested clinically in personality changes, posterior paresis, nystagmus and seizures (Pedersen, 1976; Kornegay, 1978). Lesions in the brain and spinal cord consist of pyogranulomatous meningitis, encephalitis and ependymitis (Slauson and Finn, 1972; Legendre and Whitenack, 1975; Kornegay, 1978). Inflammation of choroid plexuses and the mesencephalic aqueduct results in blockage of normal CSF flow and secondary hydrocephalus (Krum, Johnson and Wilson, 1975; Barlough and Summers, 1984). In the present investigations, CNS lesions showed a different pattern of localization compared with FIP. There was no predilection for choroid plexuses and ependyma. Vasculitis, a common finding in FIP, was not present.

Although cases of pure neurological FIP exist, most cats also have involvement of the eyes and/or other organs (Kornegay, 1978). In the present investigation, all major lesions were confined to the CNS. The results of serological investigation for coronavirus antibodies do not support the view that FIPV or other coronaviruses are plausible aetiological agents in feline non-suppurative meningoencephalomyelitis. The finding of a coronavirus antibody titre of 1 in 320 in one cat is not significant since titres of this size are also seen in many cats that have had previous infections with feline enteric coronavirus (FECV), a virus closely related to FIPV (Pedersen, 1991a).

Feline leukaemia virus (FeLV) has been reported as a cause of encephalitis in cats (Sottiaux and Pialat, 1989). However, FeLV is more commonly associated with epidural lymphosarcoma, which is usually manifested as acute posterior paresis or paralysis (Pedersen, 1991b). Neither the serological results nor the clinical and histopathological findings in the cats with staggering disease indicate a FeLV infection.

Feline immunodeficiency virus (FIV) has emerged as an important cause of neurological disease in cats (Dow, Poss and Hoover, 1990; Sparger, 1991), often in association with clinical syndromes typical of an immunodeficient state (chronic stomatitis, enteritis, dermatitis, etc). Neurological signs include psychotic behaviour, dementia, seizures and ataxia. Brain lesions are confined

to the thalamus and midbrain, sparing the cerebral cortex and cerebellum (Dow *et al.*, 1990). Non-suppurative encephalitis with perivascular mononuclear cuffing and glial nodules is commonly observed. Antibodies against FIV were not found in the cats of the present study. Seroconversion in FIV infection may be delayed for months or even years (Sparger, 1991). Also, cats in the terminal stages of FIV infection will sometimes show undetectable concentrations of antibody. However, the absence of clinical signs of immunodeficiency in cats with staggering disease argues against FIV as a causative agent.

The nervous system in cats is susceptible to feline panleukopenia virus infection during the prenatal and early postnatal period, resulting in cerebellar hypoplasia (Greene and Scott, 1990). Both clinical and histopathological data (Csiza, de LaHunta, Scott and Gillespie, 1972) are different from the cats of this report. In addition, six of the cats with staggering disease had been vaccinated against feline panleukopenia.

Sweden is a rabies-free country and staggering disease has neither the clinical signs nor histological features typical of rabies. Aujeszky's disease (pseudorabies), which is fatal in carnivores (Dow and McFerran, 1963), is excluded because of differences in the clinical picture, absence of intranuclear acidophilic inclusion bodies in neurones and astroglia and negative immunohistochemical staining for virus antigen.

Canine distemper virus (CDV) has been reported as a cause of encephalomyelitis in tigers (Blythe, Schmitz, Roelke and Skinner, 1983). Domestic cats are susceptible to experimental infection with CDV, but natural disease has not been reported in cats (Appel, Sheffy, Percy and Gaskin, 1974). Immunohistochemical staining for CDV antigen yielded negative results in cats with staggering disease.

Encephalitis has been induced experimentally in cats with the viruses of Newcastle disease (Luttrell and Bang, 1958), Borna disease (Ihlenburg, 1966), Near Eastern equine encephalomyelitis (Daubney and Mahlau, 1957) and human poliomyelitis (Salvioli, Gotti and Sternini, 1952). It is not known whether these viruses naturally infect domestic cats, but there are no reported cases in the literature.

Keane, Parent and Little (1987) inoculated one cat intracerebrally and six cats intravenously with Powassan virus of the Flavivirus serogroup. None of the cats developed neurological signs although histological lesions of a non-suppurative encephalomyelitis were observed in two cats. Tick borne encephalitis virus (TBEV) of the Flavivirus group is transmitted by the tick *Ixodes ricinus* in Sweden. Most of the cats of the present study were allowed to roam freely outdoors in regions harbouring *Ixodes ricinus* and there is a possibility that this tick could be the vector of the aetiological agent causing staggering disease. However, cats with staggering disease have tested negative for antibodies to TBEV, which indicates that this virus and probably other related viruses of the Flavivirus serogroup can be excluded as the primary cause of the disease.

Toxoplasma gondii, the most important non-viral infectious agent causing CNS disease in cats, is ruled out because of negative immunohistochemical staining for *T. gondii* antigen, absence of tissue cysts and absence of extraneural

lesions. *Borrelia burgdorferi*, a cause of arthritis and possibly meningitis in dogs (Greene, 1990) has not been reported as a cause of neurological disease in cats. All cats tested for antibodies to *Borrelia burgdorferi* in the present study were negative.

In conclusion, the neuropathological features as well as the serological and immunohistochemical results in the cats with staggering disease are not compatible with any of the known spontaneous feline viral diseases affecting the CNS. Neither are they compatible with toxoplasmosis.

The feline meningoencephalomyelitis of the present investigation is doubtless identical with that described by Kronevi *et al.* (1974) and shows many similarities to the cases of unknown aetiology reported in Switzerland by Hoff and Vandevelde (1981).

Six cases of polioencephalomyelitis in cats were reported in the United States (Vandevelde and Braund, 1979). Clinical signs included ataxia, tremors and seizures. Although the pathological lesions in the CNS were qualitatively similar to the lesions in the cats of the present study, the localization pattern was different. In the American cats, the most severe lesions were observed in the spinal cord and consisted of a marked degeneration and loss of neurones as well as white matter degeneration.

In a German safari park, an outbreak of fatal encephalomyelitis in lions and tigers occurred in the early 1970s (Flir, 1973; Melchior, 1973). The clinical as well as the histopathological picture in these large cats closely resembled that of our cats. Many lions became more affectionate and infantile and assumed a strange staring gaze. This increased affection, a phenomenon often observed in staggering disease, is not reported as a conspicuous feature of any of the known feline infectious CNS disorders; neither is it mentioned in the other reports of feline meningoencephalomyelitis of unknown aetiology cited above. The histological features in the lions and tigers were those of non-suppurative polioencephalomyelitis, with the most severe lesions in the brainstem. Efforts to isolate virus from the CNS failed. In recent years, a further outbreak of the disease was observed in the same park (Truyen *et al.*, 1990). Attempts to isolate a virus from the CNS again failed, but feline herpes virus type 1 (FHV-1) was isolated from the tonsil of one lion. This was interpreted as an infection superimposed on the encephalomyelitis as a result of reduced resistance and was not regarded as the primary cause of the disease.

FHV-1 is well known as the cause of feline rhinotracheitis. What is against FHV-1 as the aetiological agent in staggering disease is the fact that FHV-1 is regarded mainly as a breeding cattery problem, the virus being transmitted through intimate contact between cats (Pedersen, 1991c). In contrast, staggering disease is almost unheard of in breeding catteries and does not appear to be as contagious as feline rhinotracheitis. Kittens are more severely affected by FHV-1 than adult cats, while staggering disease has not been observed in cats younger than 6 months. The role of FHV-1 in feline CNS disorders has not yet been clarified, however, and the possibility that FHV-1 or related herpesviruses could be involved in the cause of staggering disease remains open.

In conclusion, some previously recorded cases of idiopathic, feline, non-

suppurative meningoencephalomyelitis presented clinical and pathological similarities to our cases suggesting a common or related aetiology. Viral infection is the most likely cause of staggering disease. The possibility of an arthropod-borne mode of transmission has been suggested. Given the consideration that most cats were freely roaming outdoors, rodents could be alternative sources of infection since they are the hosts of some neurotropic viruses, e.g. Theiler's virus and lymphocytic choriomeningitis virus. Another possible mode of transmission may be through bites and scratches exchanged between cats in fights over territory. Inoculation by bite wounds has been shown to be the major mode of transmission of feline immunodeficiency virus (FIV) and the fact that male cats are more often affected by staggering disease than females gives some support to the theory that staggering disease could be transmitted by bites in a similar way.

Further serological and virological investigations in order to identify the cause of the presently described feline non-suppurative meningoencephalomyelitis are required. This work is now in progress.

Acknowledgments

The author is grateful to the staffs of the Departments of Virology, Pathology and Bacteriology of the Swedish National Veterinary Institute for carrying out the serological and immunohistochemical investigations. Thanks are due to Dr Per Bierke for assistance with evaluation of the lymphatic tissues and to Drs Egenvall, Stavenborn and Tistedt of the Department of Medicine and Surgery, Faculty of Veterinary Medicine, for performing clinical examination of cats with staggering disease. This work was supported by grants from the Albert Hjärre Foundation, AGRIA Insurance Company and the Swedish Fund for Research without Animal Experiments.

References

Appel, M., Sheffy, B. E., Percy, D. H. and Gaskin, J. M. (1974). Canine distemper virus in domesticated cats and pigs. *American Journal of Veterinary Research*, **35,** 803–806.

Barlough, J. E. and Summers, B. A. (1984). Encephalitis due to feline infectious peritonitis virus in a twelve-week-old kitten. *Feline Practice*, **14,** 43–46.

Blythe, L. L., Schmitz, J. A., Roelke, M. and Skinner, S. (1983). Chronic encephalomyelitis caused by canine distemper virus in a Bengal tiger. *Journal of the American Veterinary Medical Association*, **183,** 1159–1162.

Borland, R. and McDonald, N. (1965). Feline encephalomyelitis. *British Veterinary Journal*, **121,** 479–483.

Burgess, E. C. (1986). Experimental inoculation of dogs with *Borrelia burgdorferi*. *Zentralblatt für Bakteriologie, Mikrobiologie und Hygiene (A)*, **263,** 49–54.

Csiza, C. K., de LaHunta, A., Scott, F. W. and Gillespie, J. H. (1972). Spontaneous feline ataxia. *Cornell Veterinarian*, **62,** 300–322.

Daubney, R. and Mahlau, E. A. (1957). Near-Eastern equine encephalomyelitis. *Nature (London)*, **179,** 584–585.

Dow, C. and McFerran, J. B. (1963). Aujeszky's disease in the dog and cat. *Veterinary Record*, **75,** 1099–1102.

Dow, S. W., Poss, M. L. and Hoover, E. A. (1990). Feline immunodeficiency virus: a neurotropic lentivirus. *Journal of Acquired Immune Deficiency Syndromes*, **3,** 658–668.

Fenner, W. R. (1989). The neurologic evaluation of patients. In *Textbook of Veterinary Internal Medicine*, Vol. 1, 3rd Edit. S. J. Ettinger, Ed., W. B. Saunders Co., Philadelphia, pp. 549–577.

Flir, K. (1973). Encephalomyelitis bei Grosskatzen. *Deutsche Tierärztliche Wochenschrift*, **80,** 401–404.

Greene, C. E. and Scott, F. W. (1990). Feline panleukopenia. In *Infectious Diseases of the Dog and Cat.* W. B. Saunders Co., Philadelphia, pp. 291–299.

Greene, R. T. (1990). Lyme borreliosis. In *Infectious Diseases of the Dog and Cat.* C. E. Greene, Ed., W. B. Saunders Co., Philadelphia, pp. 508–514.

Gutter, A., Wells, S. and Baskin, G. (1983). Neurologic disease in three cats at the Audubon Park Zoo. Proceedings, Annual meeting, American Association of Zoo Veterinarians, Tampa, Florida, October 24–27, pp. 21–26, M. E. Fowler, Ed.

Hirth, R. S. and Nielsen, S. W. (1969). Pathology of feline toxoplasmosis. *Journal of Small Animal Practice*, **10,** 213–221.

Hoff, E. J. and Vandevelde, M. (1981). Non-suppurative encephalomyelitis in cats suggestive of a viral origin. *Veterinary Pathology*, **18,** 170–180.

Ihlenburg, H. (1966). Experimentelle Prufung der Empfänglichkeit der Katze fur das Virus der Bornaschen Krankheit. *Archiv für Experimentelle Veterinärmedizin*, **20,** 859–864.

Keane, D. P., Parent, J. and Little, P. B. (1987). California serogroup and Powassan virus infection of cats. *Canadian Journal of Microbiology*, **33,** 693–697.

Kornegay, J. N. (1978). Feline infectious peritonitis: the central nervous system form. *Journal of the American Animal Hospital Association*, **14,** 580–584.

Kronevi, T., Nordström, M., Moreno, W. and Nilsson, P. O. (1974). Feline ataxia due to nonsuppurative meningoencephalomyelitis of unknown aetiology. *Nordisk Veterinärmedicin*, **26,** 720–725.

Krum, S., Johnson, K. and Wilson, J. (1975). Hydrocephalus associated with the noneffusive form of feline infectious peritonitis. *Journal of the American Veterinary Medical Association*, **167,** 746–748.

Kunz, C., Hofmann, H. and Dippe, H. (1971). Die Frühdiagnose der Frühsommermeningoenzephalitis (FSME) im Hämagglutinationshemmungstest durch Behandlung des Serums mit 2-Mercaptoäthanol. *Zentralblatt für Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene (A)*, **218,** 273–279.

Leestma, J. E. (1991). Viral infections of the nervous system. In *Textbook of Neuropathology*, 2nd Edit. R. L. Davis and D. M. Robertson, Eds, Williams and Wilkins, Baltimore, pp. 804–903.

Legendre, A. M. and Whitenack, D. L. (1975). Feline infectious peritonitis with spinal cord involvement in two cats. *Journal of the American Veterinary Medical Association*, **167,** 931–932.

Luttrell, C. N. and Bang, F. B. (1958). Newcastle disease encephalomyelitis in cats. *Archives of Neurology and Psychiatry*, **79,** 647–657.

McGaughey, C. A. (1953). Infectious myelitis of cats: preliminary communication. *Ceylon Veterinary Journal*, **1,** 38–40.

Martin, L. A. and Hintermann, J. (1952). Sur l'existence, au Maroc, d'une maladie contagieuse du Chat, non encore décrite: La Myélite infectieuse. *Bulletin de l'Academie Véterinaire de France*, **25,** 387–392.

Melchior, G. (1973). Meningo-enzephalitis beim Löwen und Tiger. In *Erkrankungen der Zootiere, Verhandlungsbericht des XV. Internationalen Symposiums uber die Erkrankungen der Zootiere.* Ippen and Schröder, Ed., Akademie-Verlag, Berlin, pp. 245–254.

Pedersen, N. C. (1976). Feline infectious peritonitis: something old, something new. *Feline Practice*, **6,** 42–51.

Pedersen, N. C. (1991a). Feline infectious peritonitis virus infection. In *Feline Husbandry: Diseases and Management in the Multiple-Cat Environment.* P. W. Pratt, Ed., American Veterinary Publications, Goleta, pp. 196–206.

Pedersen, N. C. (1991b). Feline leukemia virus infection. In *Feline Husbandry: Diseases and Management in the Multiple-Cat Environment.* P. W. Pratt, Ed., American Veterinary Publications, Goleta, pp. 210–222.

Pedersen, N. C. (1991c). Feline herpesvirus type-1 infection. In *Feline Husbandry: Diseases and Management in the Multiple-Cat Environment.* P. W. Pratt, Ed., American Veterinary Publications, Goleta, pp. 187–193.

Salvioli, G., Gotti, D. and Sternini, G. (1952). Effetti polimorfi nel gatto da inoculazione di materiale poliomielitico. *Rivista dell'Istituto Sieroterapico Italiano*, **27,** 225–245.

Slauson, D. O. and Finn, J. P. (1972). Meningoencephalitis and panophthalmitis in feline infectious peritonitis. *Journal of the American Veterinary Medical Association*, **160,** 729–734.

Sottiaux, J. and Pialat, J. (1989). Méningo-encéphalite associée a une infection FeLV chez un chat. *Pratique médicale et chirurgicale de l'Animal de Compagnie*, **24,** 635–643.

Sparger, E. E. (1991). Feline immunodeficiency virus. In *Consultations in Feline Internal Medicine*. J. R. August, Ed., W. B. Saunders Co., Philadelphia, pp. 543–550.

Sternberger, L. A. (1979). *Immunocytochemistry*, 2nd Edit. John Wiley & Sons Inc, New York.

Ström, B. (1992). Vingelsjuka hos katt ("Staggering disease" in the cat). Fördjupningsarbete. *Svensk Veterinärtidning*, **44,** 19–24.

Truyen, U., Stockhofe-Zurwieden, N., Kaaden, O. R. and Pohlenz, J. (1990). A case report: encephalitis in lions. Pathological and virological findings. *Deutsche Tierärztliche Wochenschrift*, **97,** 89–91.

Vandevelde, M. and Braund, K. G. (1979). Polioencephalomyelitis in cats. *Veterinary Pathology*, **16,** 420–427.

[*Received, May* 14*th*, 1992
Accepted, September 1*st*, 1992]