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A Retrospective Study of 286 Cases of Neurological Disorders of the Cat

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Summary

Archive central nervous tissue from 286 cats with neurological disorders was reviewed for histological evidence of feline spongiform encephalopathy (FSE), which may have occurred before it was first recognized in 1990. The following six categories of disease were identified: congenital; degenerative; inflammatory; neoplastic; FSE; lesion-free. The largest category (inflammatory) contained 92 cats, of which 47 were considered to be consistent with infection by feline infectious peritonitis (FIP) virus. Six cats showed evidence of more than one disease process; thus, one cat with FIP also had toxocara infection of the lateral ventricles and five cats with FSE also showed perivascular cuffing suggestive of concurrent viral infection. In only two cases did the diagnosis on review differ significantly from the original interpretation. There was no evidence of FSE before the original case was recognized in April 1990.

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Introduction

The causes of nervous disorders in cats are well documented in standard texts (Hopkins, 1992; Jubb and Huxtable, 1993; Summers et al., 1995), but to our knowledge there are no reports of surveys of nervous diseases in the cat.

Feline neurological disease accounts for approximately 10% of total cat referrals (i.e., approximately 60 cases per annum) to the Feline Centre, University of Bristol Veterinary School (Gruffydd-Jones, unpublished data) and a specific clinical diagnosis is made in only 30–40% of cases. In 1990, feline spongiform encephalopathy (FSE) was identified as a cause of nervous disease in cats (Wyatt et al., 1990, 1991; Wyatt, 1991). It was subsequently shown that FSE had the characteristics of a transmissible spongiform encephalopathy (TSE) (Pearson et al., 1992) and that in mouse transmission studies its behaviour was similar to that of bovine spongiform encephalopathy (BSE) (Fraser et al., 1994). At that time the archive of post-mortem diagnoses of feline neurological cases was briefly reviewed (Pearson et al., 1993), but detailed histopathological examination was not undertaken. More recently, serological and molecular evidence of exposure of cats in the UK to Borna disease virus (BDV) has been reported (Reeves et al., 1998). The aims of this study were (1) to extend the preliminary retrospective survey of the Bristol University archive of cats with neurological disease, (2) to review the histology of cases of nervous disorders, (3) to categorize the nature of the pathological changes, and (4) to search for histological evidence that FSE may have occurred in the UK before it was first recognized in 1990.

Materials and Methods

Specimens

 Archived feline specimens were obtained from the Division of Veterinary Pathology, Infection and...
Immunity. The specimens were collected during the period 1975 to December 1998. In all, 301 cases of feline neurological disease in cats were identified, consisting of 234 cases referred from the University of Bristol Veterinary School, and 67 submitted mainly as formalin-fixed tissues from outside practitioners. However, in 11 cases no central nervous system (CNS) material had been collected, and in a further four the original tissues, blocks or slides were unavailable. As a result, the cases from which histological sections were available for review numbered 286. The material examined, which varied between cases, is summarized in Table 1. In 1990 the sampling procedure was standardized to include brain sections from the anterior cerebrum, mid-cerebrum (thalamic level), posterior cerebrum (including the midbrain), cerebellum and medulla at the level of the obex.

The breeds represented in the 286 cases were: Domestic shorthair (172), Siamese (27), Domestic longhair (22), Burmese (19), Birman (13), Persian (8), Rex (4), miscellaneous (19) and unknown (2).

Histology and Electron Microscopy

Paraffin wax sections (8 μm) of formalin-fixed nervous tissues were stained with haematoxylin and eosin (HE) and examined by light microscopy. In two cases, brain tissue cut from the original blocks was dewaxed, processed in alcohol, and placed in 0.1 M sodium cacodylate buffer before being processed by routine methods for electron microscopy (EM). The various diagnoses made were compared with those in the original reports.

Results

The histological lesions in the 286 cases were classified under the following six headings: congenital; degenerative (including feline dysautonomia syndrome [FDS]); inflammatory or lesions of infectious diseases (including feline infectious peritonitis [FIP], toxoplasmosis and cryptococcosis); neoplasia (including lymphoma); FSE; no detectable lesions. The results of the 286 case reviews generally accorded with the original reports, with only occasional discrepancies. Such discrepancies are mentioned in the account below.

Congenital Lesions

This group consisted of 12 cats, all under 2 years of age. The mean age was 18.7 weeks with a median age of 12 weeks. The most common diagnoses in this group were cerebellar hypoplasia (four cats) and lysosomal storage diseases (three cats) (Fig. 1). Storage disorders were identified by the presence of many swollen abnormal neuronal cell bodies (Summers et al., 1995). In one kitten, electron microscopy and histochemical stains supported the initial diagnosis, and biochemical analysis of tissue (Dr Bryan Winchester, personal communication) confirmed the storage disorder to be a GM1 gangliosidosis (Barker et al., 1986). In another case the diagnosis was confirmed by thin layer chromatography but no detailed information was available. A dermoid cyst present at the level of the third thoracic vertebra of a 16-month-old cat resulted in ataxia and euthanasia (Henderson et al., 1993). The remaining diagnoses included one case each of hypomyelinogenesis, neuraxonal dystrophy, syringomyelia and cerebellar abiotrophy.

Degenerative Lesions Including Feline Dysautonomia

Degenerative lesions other than those of FDS. These accounted for 42 cats mainly mature animals but ranging in age from 5 weeks to 19 years (mean 4.5 years). The changes present included Wallerian degeneration of brain or spinal cord (or both), white matter spongy degeneration, and myelin oedema. Three cats with hepatic encephalopathy due to portosystemic shunts were included in this group because, although the shunt may have developed as a congenital lesion, the CNS lesion was degenerative rather than of a primary congenital type.

Feline dysautonomia. This affected 27 cats, mainly in the younger age range (median age 12 months; mean age 18 months). The majority of cases (23) were diagnosed between 1982 and 1986, with only four cases diagnosed subsequently. Diagnostic features included loss and degeneration of neuronal cell bodies within sympathetic ganglia, with a variable infiltrate of mononuclear cells.

| Sites                                      | Number of cats |
|-------------------------------------------|----------------|
| Brain                                     | 120            |
| Spinal cord                               | 22             |
| Brain and spinal cord                     | 89             |
| Brain and spinal cord + other tissue, e.g., eye, tumour mass | 10             |
| Brain (but not spinal cord) + other tissue, e.g., eye, tumour mass | 11             |
| Ganglia only                              | 18             |
| Ganglia and brain or spinal cord, or both | 11             |
| Tumour mass (meningioma)                  | 5              |

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**Table 1**

Histological sections (from 286 cats) reviewed
Brain tissue was examined in 10 of these cases, one of which showed mild vacuolation of the white matter in the obex region, but no other lesions affecting brain or spinal cord of the remaining cats with typical ganglionic lesions were identified.

Inflammatory Lesions or Lesions of Infectious Diseases

The 92 cats affected had a mean age of 5.7 years. They included 47 FIP cases (mean age 18 months; median age 10 months). Burmese cats with FIP \((n = 8)\) were over-represented in relation to the proportion of animals of this breed in the overall study (19 of 268 cats).

Typical inflammatory lesions included perivascular cuffing and meningeal infiltration by mononuclear cells, gliosis, and variable neuronal degeneration suggestive of a possible underlying viral aetiology. In cats in which the inflammation tended to be pyogranulomatous, located around the lateral ventricles or in the meninges, or affecting the choroid plexus, with or without
evidence of vasculitis or hydrocephalus, a diagnosis of FIP was made. In one of these cats there was concurrent infection by *Toxocara* larvae within dilated lateral ventricles (Fig. 2).

Of the 45 remaining cases (i.e., non-FIP cats) eight had protozoal tissue cysts (presumed but not confirmed to represent toxoplasmosis; Fig. 3) and one had cryptococcosis (confirmed by culture; Fig. 4). Protozoal infection and cryptococcal meningitis tended to affect middle-aged or older cats; however, the youngest animal with protozoal infection was only 2 months old. A single large protozoal cyst, unassociated with any inflammatory response, was identified in the hippocampus of a Persian cat with FSE (see below) and was considered to be an incidental finding.

Bacterial infection was identified in three cats, two of which had a meningoencephalitis associated with bacterial colonies; in the third case the infiltrate was suggestive of a bacterial meningitis and bacteria were identified by electron microscopy (Fig. 5).

In the remaining 33 cats a diagnosis of meningitis or encephalitis, or both, was made. A specific diagnosis was not possible in many cases, but in one cat immunohistochemical examination had
identified feline immunodeficiency virus (FIV) infection associated with giant cells within the brain (Fig. 6) (Gunn-Moore et al., 1996).

There may be some difficulty in distinguishing FIP infection from other forms of viral infection, and eight cats were identified in which the original diagnosis had been of a meningoencephalitis but which, on review, were considered to have features consistent with a diagnosis of FIP. One cat had originally been found (correctly) to have hydrocephalus, but the periventricular and choroid plexus pyogranulomatous inflammation also present had not been reported. On review, therefore, this cat was considered most likely to have been infected by FIP virus. Conversely, another cat, originally thought to have FIP, was considered on
review to have lesions of a less specific nature, due to some other, possibly viral, agent.

**Neoplasia**

Thirty-eight cases of neoplasia were seen, of which 18 were diagnosed as lymphoma. Cats with lymphoma tended to be younger (mean age 3.75 years) than those with other forms of neoplasia (mean age 6.9 years). The distribution of lymphoma within the CNS is shown in Table 2. Lymphoma was located within the spinal canal in 13 cats; four of which also had neoplastic infiltrates in the brain. The brain alone was affected in the remaining five cats. Twelve of the 18 cats with lymphoma also showed evidence of lymphoma affecting other sites, e.g., kidney, liver, lymph node and vertebrae.

In the remaining 20 cases (neoplasia other than lymphoma), meningioma was the most common tumour (12 cats; six with single cranial meningioma, two with multiple cranial meningioma, and four with spinal meningioma). There were, in addition, four cases of gloma (one of which had previously been diagnosed as an inflammatory lesion), three cases of sarcoma and one of metastatic carcinoma secondary to a bronchoalveolar carcinoma.

**Feline Spongiform Encephalopathy (FSE)**

FSE was diagnosed in 24 cats, with an average age of 6 years. FSE lesions were absent in the brains of 136 cats which died before recognition of the first case of FSE by Wyatt *et al.* (1990); after this first case, however, 23 of 149 cats examined post mortem were found to have FSE. The diagnosis was confirmed by demonstrating typical lesions in the brain and spinal cord, consisting of: widespread neuropil vacuolation, particularly of the grey matter; neuronal vacuolation, with one or multiple empty vacuoles, throughout the CNS but particularly in the thalamus, midbrain, obex and spinal cord; astrocytic hyperplasia and hypertrophy (Wyatt *et al.*, 1991). In five cats, there was also evidence of mild perivascular cuffing (Fig. 7) in the cerebrum or medulla, or both, and in one of these five animals focal accumulation of lymphoid cells in the meninges of the brain and spinal cord. One of these five cats also had a large protozoal cyst within the hippocampus, without any inflammatory reaction (see above). The dual presence in these five animals of FSE lesions and lesions indicative of

| Site                                      | Number of cases |
|-------------------------------------------|-----------------|
| Extradural to spinal cord                 | 5               |
| Spinal cord meninges                      | 2               |
| Spinal cord parenchyma                    | 2               |
| Brain meninges                            | 1               |
| Brain parenchyma                          | 4               |
| Meninges of brain and spinal cord         | 2               |
| Meninges and parenchyma of brain and spinal cord | 2           |

Fig. 7. Cat brain, thalamus. Feline spongiform encephalopathy with possible co-existent viral infection, indicated by perivascular lymphoid cuff (lower right). Vacuolated neuron (arrow). HE. × 400.
possible viral infection suggests the presence of more than one disease process.

No Detectable Lesions
Fifty-one cats (17.8% of the 286 examined) showed no lesions either at the initial examination or at the review. The sections examined were of brain alone (33 cats), brain and spinal cord (11 cats), spinal cord alone (two cats), and ganglia (two cats).

Discussion
Detailed histological investigation of the archive indicated that in the majority of cases there was agreement between the original histological descriptions and diagnoses, and those following re-examination of the slides. However, occasional discrepancies were found. In one cat with hydrocephalus and an inflammatory infiltrate typical of FIP (Krum et al., 1975), the original description did not include reference to the inflammatory infiltrate. A second cat was originally reported to have an inflammatory and degenerative lesion of the midbrain and medulla, but on review the lesion was considered to be associated with a pleomorphic tumour (possibly a glioma of the astrocytoma type). The cells were variable in appearance and it would seem were originally interpreted as purely inflammatory. Other cases in which the original and final diagnoses differed were more difficult to interpret. These cats included five in the group with degenerative changes; in these animals the lesion distribution or appearance suggested viral infections such as FIV (Poli et al., 1997), although glosis did not appear to be a feature. In addition, there may have been overlap between the inflammatory lesions associated with FIP virus and with other viral agents. Other techniques (e.g., immunohistochemistry) might have helped to classify these cases further.

In six cats there was evidence of more than one lesion pattern or disorder. Five of these cats had characteristic lesions of FSE (Wyatt et al., 1991) as well as evidence of perivascular cuffing suggestive of concurrent viral infection. One of these, which had a high coronavirus antibody titre suggestive of infection by FIP, was reported by Reeves et al. (1998) to have given a positive polymerase chain reaction (PCR) result for Borna disease virus (BDV) in one of three tests on brain tissue, but this was considered an equivocal finding. The sixth cat had inflammatory lesions consistent with FIP, including dilation of the lateral ventricle. In addition the lateral ventricles contained nematode (Toxocara) larvae. This was probably merely an incidental finding, but it may nonetheless have contributed to the ventricular dilation.

The largest combined group of cats included those with evidence of inflammatory lesions within the CNS. Approximately 50% (47) had lesions consistent with a diagnosis of FIP (Krum et al., 1975; August, 1984). Of the remainder, the majority had a non-suppurative encephalitis or meningoencephalitis suggestive of viral infection (Summers et al., 1995). Bacterial infection, toxoplasmosis and cryptococcosis also produce inflammation and degeneration within the CNS and may be associated with infection by other viruses, e.g., FIV or feline leukaemia virus (FeLV) (Gerds-Grogan and Dayrell-Hart, 1997). In cats with CNS inflammatory lesions suggestive of viral infection, immunohistochemical and molecular techniques would probably be of diagnostic value.

The largest single category consisted of 51 cats for which no CNS abnormality could be detected. It is possible that an underlying physiological or metabolic defect resulted in neurological signs without producing recognizable histological changes (Summers et al., 1995), or that localized lesions occurred but were not included in the histological sections.

Congenital lesions, not surprisingly, were seen mainly in young cats, cerebellar hypoplasia and lysosomal storage disorders being the most common findings. GM1 gangliosidosis was confirmed in two cats, one of which showed biochemical features similar to those of GM1 gangliosidosis type 1 (Barker et al., 1986). Feline dysautonomia, also seen mainly in young cats, was first recognized in 1981 (Key and Gaskell, 1982). Significant numbers of cats were affected in the early 1980s, but cases are now diagnosed infrequently. The cause is not known but a toxic or infectious aetiology is most likely (Summers et al., 1995). The CNS is rarely affected and the diagnosis is made from examination of ganglia. This was reflected in the present study.

Degenerative conditions of the CNS encompass a diverse group of disorders, some of which may be due to infectious agents. For example, white matter vacuolation may be due to FIV infection (Poli et al., 1997). Metabolic causes include hepatic encephalopathy, organophosphorus intoxication and ischaemia. A limited range of CNS lesions may occur in response to a wide range of factors; this fact often complicates diagnosis (Summers et al., 1995).

Meningioma was the most frequently diagnosed primary tumour of the CNS (12 cats out of 22). These neoplasms, which occurred in the cranium or spinal canal, or both, included two cases of
multiple cranial meningioma. The distribution was similar to that found in other studies (Gavin et al., 1995). Lymphoma, a common CNS neoplasm, tends to occur in the spinal canal more often than the cranium (Wheeler, 1989). Of the 18 lymphomas identified in this study: nine were confined to the spinal canal (seven being confined to the spinal canal or meninges, and two to the cord); four were confined to the brain; one was confined to the brain meninges; and four were present in both the brain and spinal canal. The present findings are therefore in accordance with those of Wheeler (1989). Neoplastic cells may be present subdurally, causing compression of the cord and secondary degeneration, or may infiltrate the parenchyma causing direct damage. Eight cats in this study had meningeal or extradural lymphomatous infiltrates with secondary cord compression. Lymphoma affecting the CNS is often part of a generalized disease (Wheeler, 1989).

This detailed study confirmed that in cats with clinical signs of neurological disease the most frequent diagnostic category was “inflammation” (32%). In 17.8% of cases, however, histological changes were absent in the CNS sections examined. In six cats there was evidence of more than one disease process. Furthermore, there was no histological evidence of any cat with FSE before recognition of the first case in 1990 (Wyatt et al., 1990, 1991). Therefore, the original detection of FSE was not due merely to increased awareness of TSEs: it was due to the sudden appearance of a disease that had not previously existed.

In five of the cats found to have FSE since the original cases reported by Wyatt (1991) and Wyatt et al. (1991, 1993), there was also perivascular cuffing suggestive of concurrent viral infection. Evidence of possible dual infection has been observed in cases of BSE in cattle (S. Ryder, personal observation). Borna disease virus is associated with a non-suppurative meningoencephalitis in horses and other species (Rott and Becht, 1995) and is considered by some to be the cause of “staggering disease” in cats (Lundgren et al., 1995). No specific clinical signs or neurological lesions of Borna disease have yet been demonstrated in cats in the United Kingdom, but this requires further investigation.

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