

# Papers

## Infectious canine hepatitis in red foxes (*Vulpes vulpes*) in the United Kingdom

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**The pathological findings are described in three cases of infectious canine hepatitis in free-ranging red foxes (*Vulpes vulpes*) in England. The foxes died after short periods of clinical illness. Mild jaundice and hepatic congestion were evident grossly. On histopathological examination, intranuclear inclusion bodies were visible in hepatocytes, in association with hepatocyte dissociation and necrosis, as well as in renal glomeruli, renal tubular epithelial cells and vascular endothelial cells. Canine adenovirus type 1 (CAV-1) was isolated from all three foxes. In a serological study, antibodies to CAV-1 were detected in tissue fluid extracts taken from 11 of 58 (19 per cent) frozen red fox carcasses from England and Scotland.**

INFECTIOUS canine hepatitis (ICH), caused by canine adenovirus type 1 (CAV-1), has been reported mostly in domestic dogs, farmed foxes and other captive carnivores; there are few reports of spontaneous ICH in free-ranging animals (Woods 2001). Originally referred to as distemper or epizootic fox encephalitis, ICH was first identified in North America in domesticated ('tamed') silver foxes, a colour variant of the red fox (*Vulpes vulpes*) (Green 1925, Green and others 1930). Spontaneous ICH has also been reported in farmed Arctic (blue) foxes (*Alopex lagopus*) (Kummeneje 1971, Shcherbatykh and Sonin 1971).

Red foxes and grey foxes (*Urocyon cinereoargenteus*) are susceptible to experimental infection with CAV-1 (Green and Stulberg 1930). The first reported case of spontaneous ICH in a free-ranging grey fox was identified in 2004 in Georgia, USA (Gerhold and others 2007). Although ICH is thought to occur in free-ranging red foxes submitted to wildlife rescue centres in England (Stocker 2005), there are no confirmed reports of spontaneous ICH in red foxes.

There is serological evidence of exposure to CAV-1 in free-ranging red foxes in North America, Germany and Australia (Amundson and Yuill 1981, Truyen and others 1998, Robinson and others 2005), as well as in free-ranging grey foxes in North America (Riley and others 2004); however, there are no published serological studies of CAV-1 in red foxes in the UK.

This paper describes the pathological findings and results of virological investigations in three cases of ICH in free-ranging red foxes in England. It also reports the results of serological testing for antibodies to CAV-1 in tissue fluids from red fox carcasses in England and Scotland.

### Materials and methods

#### History and pathological examinations

One free-ranging juvenile female red fox (case 1) was admitted to Tigglywinkles Wildlife Hospital, Buckinghamshire, in September 1995. Two red foxes (cases 2 and 3), whose age and sex were not recorded, were submitted to a veterinary practice in Cheshire in May 2000. All three foxes died within two days of admission.

Samples of liver, kidney, spleen and lymph node from each fox were collected at postmortem examination; samples of intestine were also collected from cases 2 and 3. Tissue samples were submitted to the University of Glasgow from the International Zoo Veterinary Group, Keighley, and from MacDonald Exotic and Domestic Laboratories (MedLab), Tarporley. Tissues were fixed in 10 per cent neutral buffered formalin, dehydrated in graded ethanol solutions and embedded in paraffin wax. Histological sections (4 µm thick) were stained with haematoxylin and eosin for histopathological examination.

#### Virus isolation from fox tissues

Madin-Darby canine kidney (MDCK) cells from laboratory stocks in the Canine Infectious Diseases Research Unit at the University of Glasgow (Cornwell and others 1970) were grown to 80 per cent confluency in polystyrene flasks (Nunc) in tissue culture medium consisting of Eagle's minimum essential medium (MEM) containing 5 per cent fetal bovine serum (heat-inactivated at 56°C for 30 minutes), 400 mg/ml streptomycin, 400 U/ml penicillin, 2 mM L-glutamine (Life Technologies, Gibco BRL) and MEM Non-essential Amino Acid Solution 100x (Sigma-Aldrich). Cells were harvested using 0.25 per cent trypsin (Sigma-Aldrich) and 1M EDTA in PBS. The cells were counted using a Neubauer chamber and suspensions were diluted in tissue culture medium. Each well of a 12-well tissue culture plate (Nunc) was seeded

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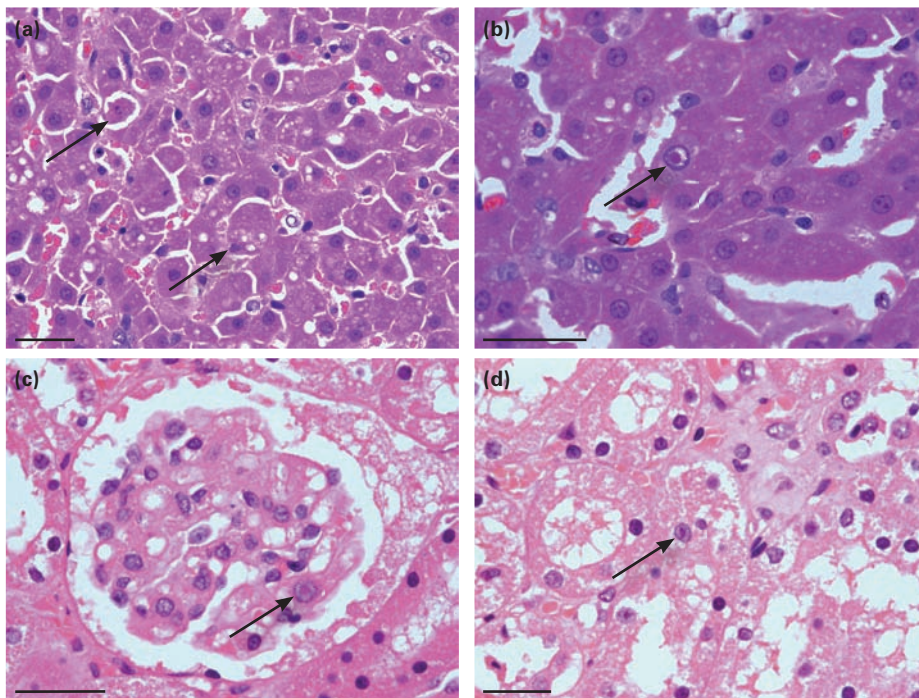


FIG 1: Histopathology of the liver and kidney of a red fox (case 2) with infectious canine hepatitis. (a) Dissociation and necrosis (arrows) of hepatocytes. (b) Intranuclear inclusion body (arrow) in an hepatocyte. (c) Intranuclear inclusion body (arrow) in a renal glomerulus. (d) Intranuclear inclusion body (arrow) in a renal tubular epithelial cell, along with renal tubular necrosis. Haematoxylin and eosin. Bars = 50 µm

with  $1 \times 10^5$  MDCK cells in 1 ml tissue culture medium and incubated at 37°C for two hours until the cells were adherent.

Fresh samples of liver were collected from each of the three affected foxes at postmortem examination and transported chilled for virus isolation. Tissue homogenates were prepared by grinding approximately 0.5 g fresh liver, using a sterile mortar and pestle, with 500 µl tissue culture medium. The homogenates were centrifuged at 900 g for 10 minutes in a J2-21 centrifuge with a JA-20 fixed angle rotor (Beckman Instruments). Supernatant (50 µl per well) was inoculated into selected wells in 12-well tissue culture plates containing MDCK cells with 450 µl tissue culture medium and incubated at 37°C for two hours. The inoculum in each well was then removed and replaced with 1.5 ml tissue culture medium warmed to 37°C. The plates were incubated at 37°C for four days and examined daily for cytopathic effects (cpe).

As a positive control, 50 µl of CAV-1 laboratory stock containing 100 50 per cent tissue culture infectious doses ( $TCID_{50}$ ) of virus was added to 12-well tissue culture plates and diluted with tissue culture medium to a final concentration of 30  $TCID_{50}$ /µl in a total volume of 1.5 ml. The cpe in wells from positive control and test inocula were neutralised using canine polyclonal antisera containing specific antibodies to CAV-1 but negative for CAV-2, canine distemper virus, canine parvovirus and canine parainfluenza virus (CPiV), as described below. Cells were also tested for haemadsorption of canine erythrocytes to exclude infection with CPiV.

#### Extraction of fluids from tissue samples from foxes

In a separate serological study, antibodies to CAV-1 were determined using a virus neutralisation test (VNT) applied to tissue fluids extracted from muscle and lung tissue of 58 British red fox carcasses using the method of Nielsen and others (1998). The fox carcasses had been collected in England and Scotland between October 1999 and November 2000 as part of a study investigating the presence of *Trichinella spiralis*, *Echinococcus multilocularis* and *Toxoplasma gondii* (Smith and others 2003). There were four juvenile foxes, 45 subadults and nine adults; 28 of the foxes were male and 30 were female.

The carcasses were stored frozen at -20°C and then thawed at room temperature for 72 hours. Samples of thawed tissue were collected from the semitendinosus muscle (30 g) and the lungs (20 g). The samples were again frozen at -20°C for at least 24 hours and

then thawed at 4°C. Tissue fluids were extracted from the freeze-thawed tissue samples using a sterile Pasteur pipette and then centrifuged at 10,000g for 10 minutes in a J2-21 centrifuge with a JA-20 fixed angle rotor. The supernatant was filtered through a 0.45 µm cellulose acetate filter (Acrodisc; Gelman Sciences) and the filtrate was stored at 4°C.

To validate the antibody assay for muscle tissue from foxes, samples of muscle were collected from five dogs of unknown vaccination status that were submitted for routine postmortem examination after being euthanased because of non-infectious diseases. Plasma samples from all five dogs were available from routine diagnostic investigations performed before euthanasia. Samples of lung and aqueous humour were also collected from three of these dogs. The muscle and lung samples were processed as for the tissues from the fox carcasses. Samples of aqueous humour were centrifuged at 10,000g for 10 minutes and filtered through a 0.45 µm cellulose acetate filter, as for tissue fluids. Samples of plasma and aqueous humour were stored at 4°C.

#### CAV-1 neutralisation assay

Tissue fluids, plasma samples and aqueous humour were treated at 56°C for 30 minutes to heat-inactivate complement. Using 96-well flat-bottomed tissue culture plates (Nunc), fourfold dilutions of 25 µl of each test sample were made in 75 µl tissue culture medium in each well from 1:4 to 1:16,384. Each sample was replicated four times on the same plate. Control samples of positive and negative canine sera were included on each plate. CAV-1 stock virus (strain 47889) was added to each well at a final concentration of 100  $TCID_{50}$ /100 µl. The plates were incubated at 37°C for 60 minutes and then for a further 60 minutes at room temperature. MDCK cells (50 µl containing  $1 \times 10^6$  cells/ml) were added to each well and incubated at 37°C for five days in a humidified incubator containing 5 per cent carbon dioxide. The plates were examined microscopically for cpe to determine the endpoint of each titration. The antibody titre was calculated from the inverse of the endpoints across four replicates.

As part of the standardisation of the method, the samples from five dogs were also tested for CAV-2 using 100  $TCID_{50}$ /100 µl laboratory stock virus (Manhattan strain); CAV-2 is used in current canine vaccines. The samples from foxes were not tested for CAV-2.

## Results

### Clinical signs

Case 1 was collapsed, jaundiced and died on the day of admission. Cases 2 and 3 were depressed and exhibited mild jaundice at the time of admission. Case 2 died after one day and case 3 died after two days, without other clinical signs being noticed by the animal handlers in either case.

### Gross pathology

All three foxes were mildly jaundiced and had congested livers, with mild accentuation of the hepatic lobular pattern. The mesenteric and hepatic lymph nodes were mildly enlarged and congested.

### Histopathology

Histopathological examination of the liver from all three foxes revealed generalised necrosis and dissociation of hepatocytes (Fig 1a). Multifocal hepatic necrosis was also evident, especially in case 3. Intranuclear inclusion bodies typical of CAV-1 were visible in hepatocytes (Fig 1b) and occasionally in renal glomeruli (Fig 1c), proximal convoluted renal tubular epithelial cells (Fig 1d) and vascular endothe-

**TABLE 1: Titres of antibodies to canine adenovirus type 1 (CAV-1) in tissue fluid extracts from 11 seropositive red fox carcasses in England and Scotland\***

Fox	CAV-1 antibody titre		Source of carcass
	Lung	Muscle	
1	<8	91	West Lothian, Scotland
2	91	<8	Somerset, England
3	181	<8	West Sussex, England
4	362	91	Dumfries and Galloway, Scotland
5	256	45	Somerset, England
6	512	256	Essex, England
7	128	64	Dumfries and Galloway, Scotland
8	45	<8	West Sussex, England
9	64	32	Dumfries and Galloway, Scotland
10	91	32	Somerset, England
11	128	32	Hampshire, England

\* 47 other foxes from England and Scotland had CAV-1 antibody titres <8

lial cells. Lymphoid depletion and lymphocytolysis were observed in the spleen and lymph nodes. The intestines of cases 2 and 3 were unremarkable.

### Virology

CAV-1 was isolated from all three foxes, confirming a diagnosis of ICH. Typical cpe were observed in cell cultures and were neutralised by specific canine antiserum.

### Serology

Antibodies to CAV-1, with titres ranging from 32 to 512, were detected in tissue fluid extracts from lung and/or muscle tissue of 11 of the 58 (19 per cent) fox carcasses from England and Scotland (Table 1). In 10 of these 11 cases, antibody titres were higher in tissue fluid extracted from the lungs than in tissue fluid extracted from muscle.

All five plasma samples from dogs were positive for CAV, with titres ranging from 128 to 2896 for CAV-1 and from 24 to 2896 for CAV-2 (Table 2). In contrast, aqueous humour was negative for antibodies to CAV-1 and CAV-2 in the three dogs for which aqueous humour was available. In dogs with antibody titres above 128 in plasma, antibodies to CAV-1 were also detected in the lung and muscle samples (Table 2). Antibody titres were higher in fluid from the muscle than from the lung in two of the three dogs for which paired samples were available.

### Discussion

This study reports three cases of ICH in red foxes and also demonstrates that antibodies to CAV-1 can be detected in free-ranging red foxes in England and Scotland. These findings indicate that red foxes in Great Britain can be exposed naturally to CAV-1 and are susceptible to ICH. Cases of ICH confirmed by histopathology and virus isolation do not appear to have been reported previously in free-ranging red foxes. Fujimoto (1957) reported spontaneous ICH in foxes in Japan, but did not indicate the species of fox or whether the disease occurred in free-ranging animals. The first case of spontaneous ICH in a free-ranging grey fox was identified only recently in the USA (Gerhold and others 2007).

**TABLE 2: Titres of antibodies to canine adenovirus type 1 (CAV-1) and type 2 (CAV-2) in plasma, tissue fluid extracts and aqueous humour from five dogs**

Dog	CAV-1 antibody titre				CAV-2 antibody titre			
	Plasma	Muscle	Lung	Aqueous humour	Plasma	Muscle	Lung	Aqueous humour
1	256	128	64	<8	128	32	32	<8
2	128	<8	NS	NS	24	<8	NS	NS
3	181	256	128	<8	128	181	512	<8
4	2048	128	512	<8	181	<8	91	<8
5	2896	256	NS	NS	2896	128	NS	NS

NS Not sampled

The clinical signs and pathological findings in the three red foxes with ICH in the present study were similar to those described in other species of foxes and in dogs. Clinical signs in foxes appear after an incubation period of two to six days and may include anorexia, rhinitis, haemorrhagic diarrhoea, hyperexcitability, seizures, paralysis, coma and death (Woods 2001). Death may occur after a brief clinical course or suddenly without prior clinical signs. Uveitis and keratitis ('blue eye') may develop in non-fatal cases of ICH in silver foxes (Woods 2001). Gross lesions in foxes with ICH are considered to be less distinctive than in dogs, and generalised congestion and mild enlargement of the liver, spleen and adrenal glands have been reported (Green and others 1934, Woods 2001).

On histopathological examination, vasculitis is considered to be a prominent feature of ICH in foxes (Woods 2001), but was not a major finding in the three cases examined in the present study. Necrosis of hepatocytes and renal tubular epithelial cells is also evident in foxes with ICH, but hepatic necrosis may be less severe than in dogs (Woods 2001). Generalised hepatocyte necrosis and dissociation was observed in all three cases in this study, but marked multifocal hepatic necrosis was seen only in one case. Intranuclear inclusion bodies typical of adenovirus inclusions were found in hepatocytes in the liver, in glomeruli and proximal convoluted tubules in the kidney, and in vascular endothelial cells. The brains of the foxes in this study were not submitted for histopathological examination.

Serological studies are widely used to detect exposure to pathogens in free-ranging populations of carnivores (Cleaveland and others 2007), but the collection of blood samples from free-ranging wild animals requires capture and sedation or immediate collection of blood after animals are killed by shooting. The present study used a technique developed for the extraction of tissue fluids from the muscle of slaughtered pigs for the detection of antibodies to *Salmonella* species (Nielsen and others 1998). The results show that fluids extracted from muscle and lung tissue of carcasses of animals that have died as a result of trauma due to road traffic accidents or shooting during pest control programmes can be used for serological testing for evidence of exposure to pathogens.

To the authors' knowledge there are no other published serological studies of CAV-1 in red foxes in Great Britain. Antibodies to CAV-1 have been detected in serum from two of 57 (3.5 per cent) free-ranging North American red foxes (*Vulpes fulva*) in Wisconsin, USA (Amundson and Yuill 1981), 17 of 485 (3.5 per cent) free-ranging red foxes (*Vulpes crucigera* syn *Vulpes vulpes*) in Germany (Truyen and others 1998) and 308 of 1326 (23.2 per cent) free-ranging naturalised red foxes (*Vulpes*) in Australia (Robinson and others 2005). Serum antibodies to CAV-1 were also detected in all of 47 captive North American red foxes held illegally by a wildlife dealer in Ohio, USA (Davidson and others 1992).

In the present study, the prevalence of antibodies to CAV-1 in 58 free-ranging red foxes from England and Scotland was 19 per cent, substantially higher than the prevalence in free-ranging red foxes in the USA and Germany, and slightly lower than that reported in Australia. However, allowance must be made for differences in results because the present study used tissue fluid extracts, while other studies used serum samples collected from live or freshly shot dead foxes. The use of tissue fluid extracts is likely to be less sensitive than serum for the detection of specific antibodies to infectious agents. The red foxes with positive antibody titres to CAV-1 were from Scotland or southern England; no seropositive animals were detected from northern

England or the Midlands. Further investigation is required to determine whether there are regional differences in seropositivity for CAV-1 in red foxes in Great Britain.

Antibodies to CAV-1 have also been detected in 88 per cent of free-ranging grey foxes in the USA (Riley and others 2004). There is serological evidence of exposure to CAV-1 in several other species of fox in North and South America, including the island grey fox (*Urocyon littoralis*) (Garcelon and others 1992, Clifford and others 2006), San Joaquin kit fox (*Vulpes macrotis mutica*)

(Cypher and Frost 1999), culpeo (*Dusicyon culpaesus*) (Martino and others 2004) and Argentine grey fox (*Dusicyon griseus*) (Martino and others 2004). The prevalence of neutralising antibodies to CAV-1 in stray dogs of unknown vaccination status was 45 per cent in Japan (Shin-Ichiro and others 1960) and 50 per cent in Brazil (Carvalho and others 1975), but there have been no recent studies of CAV-1 exposure in stray dogs in Great Britain. Antibodies to CAV-1 will cross-react with CAV-2, but infection with CAV-2 has been recognised only in dogs. It is difficult to assess the relative importance of wild canids and domestic dogs as reservoirs of CAV-1 without more knowledge of the dynamics of infection in both populations.

The role of red foxes in the epidemiology of ICH in Great Britain is uncertain. It is not known whether foxes are an important reservoir for infection with CAV-1, and thus a source of infection for domestic dogs, or vice versa. In Great Britain there is a relatively high frequency of vaccination of dogs against CAV (using CAV-2-based vaccines) and stray dog populations are controlled effectively, so the risk of ICH in domestic dogs is relatively low (Böhm and others 2004). Antibody titres considered to be protective against CAV-1 (>64) were detected in 118 of 144 (82 per cent) vaccinated adult dogs in the UK that were tested three to 15 years after vaccination (Böhm and others 2004); protective antibody titres against CAV-1 were also present in 16 of 194 (8.2 per cent) puppies before vaccination (Böhm and others 2004). However, 80 cases of ICH in domestic dogs have been diagnosed at the University of Glasgow between 1986 and 2007 (unpublished data), providing evidence of ongoing exposure of susceptible dogs to CAV-1 in the UK.

This study demonstrates that spontaneous ICH occurs sporadically in red foxes in Great Britain and that there is serological evidence of natural exposure to CAV-1 in free-ranging red foxes. ICH is likely to occur in free-ranging red foxes and other species of fox in many parts of the world, but there is a low probability of detecting affected animals because of the difficulty in monitoring wild populations. There is potential for transmission of CAV-1 between foxes, dogs and other carnivores (Woods 2001). Without information on the current vaccination coverage in domestic dogs, or estimates of the basic reproduction number,  $R_0$  (the mean number of infections an infected animal will cause in a population with no immunity to the disease, in the absence of attempts to control the spread), it is not possible to determine whether free-ranging red foxes or domestic dogs are the reservoir for CAV-1. Nevertheless, given the relatively widespread uptake of vaccination against CAV in domestic dogs in the UK, wild red foxes are clearly a potential reservoir of infection for both red foxes and dogs.

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