Infectious canine hepatitis, not only in the textbooks: a brief review and three case reports

Infectieuze caniene hepatitis, niet alleen in de handboeken: een beknopt overzicht en drie gevalstudies

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ABSTRACT

Infectious canine hepatitis (IHC) caused by canine adenovirus 1 (CAdV-1) is a classic disease in dogs causing severe illness in non-vaccinated dogs. For this reason, CAdV-1 is incorporated in the standard core vaccination. Because of widespread vaccination, this disease is only rarely seen by the veterinary practitioner. However, ICH does occur in Belgium, especially when vaccination is not adequate. In this brief review, the authors intend to refresh the knowledge of ICH illustrated by three recent cases.

SAMENVATTING

Infectieuze caniene hepatitis (IHC) veroorzaakt door het caniene adenovirus 1 (CAdV-1) is een klassieke ziekte bij honden die een ernstig verloop kent bij niet-gevaccineerde honden. Om deze reden is CAdV-1 opgenomen in de standaardvaccinatie. Door de wijdverspreide vaccinatie wordt deze ziekte nog slechts zelden gezien door de dierenarts. ICH komt echter wel voor in België, vooral wanneer de vaccinatie niet adequaat is. Met deze beknopte review willen de auteurs de kennis van ICH opfrissen, geïllustreerd met drie recente gevallen.

ETIOLOGY

Canine adenovirus 1 (CAdV-1) causes infectious canine hepatitis (ICH), also called epizootic fox encephalitis or Rubarth's disease. Infection can occur in dogs but also wild *Canidae* (e.g. foxes, wolves and coyotes), *Ursidae* (bears) and *Mustelidae* (e.g. martens, weasels, sloats) can be infected (Greene, 2012; Dowgier et al., 2018). Viral shedding occurs through all secretions and excretions in the acute stage. Up to nine months post infection, the virus can persist in the kidneys with presence of the virus in the urine (Baker et al., 1954; Willis, 2000). Adenoviruses are very resistant in the environment, surviving several days at room temperature and several months at ≤4°C. Canine adenovirus 2 (CAdV-2) causes mild self-limiting infection of the upper respiratory tract and is a contributor to infectious tracheobronchitis (ITB) known as kennel cough (Greene, 2012; Day et al., 2020).

PATHOGENESIS

After oronasal exposure, viral replication causes an often severe tonsillitis and pharyngitis (Cullen and Stalker, 2016). The virus translocates in the bloodstream causing viremia and reaching its primary targets: endothelial cells and hepatocytes (William, 2000). The main organs affected by CAdV-1 are liver, kidneys and eyes (Greene, 2012). Hepatocellular viral replication causes widespread necrosis. A sufficient antibody response clears the virus and restricts the hepatic damage with complete regeneration. When a partial neutralizing antibody titer is present at 4 to 5 days post infection (dpi), persistent hepatic inflammation continues and chronic active hepatitis develops finally resulting in hepatic fibrosis. A persistently low antibody titer will result in extensive hepatic necrosis and death (Greene, 2012).

Throughout the body, the virus targets the vascular endothelial cells. In the kidneys, viral replication pri-

mary injures the capillary network of the glomerulus. Because of immune complex formation, glomerulonephritis develops with transient proteinuria (Decaro et al., 2008; Greene, 2012). In recovered dogs, the virus persists in the renal tubular epithelium resulting in urinary viral shedding for several months (Baker et al., 1954; Willis, 2000; Greene, 2012). A mild non-progressing interstitial nephritis may be present after recovery (Cullen and Stalker, 2016).

Ocular lesions develop in approximately 20% of dogs after recovering from natural disease. In a first stage, viral replication occurs in the endothelium of the anterior uvea (the iris) and the inner side of the cornea. This results in mild uveitis with often photophobia during clinical or subclinical disease (Willis, 2000). In a later stage, more severe keratouveitis with corneal edema develops. After seroconversion (at 6-7 dpi), immune complexes (type III hypersensitivity) damage the corneal endothelium causing corneal edema (‘blue eye’) (Wilcock and Njaa, 2016). No viral replication is present at this stage (Willis, 2000). In severe cases, blocking of the iridocorneal filtration angle can cause glaucoma (Greene, 2012).

A common complication of the acute disease is diffuse intravascular coagulation (DIC). DIC develops because of widespread endothelial damage with systemic intravascular blood clotting and secondary consumption of the coagulation factors and thrombocytes. Because of systemic endothelial damage and DIC, generalized petechial and ecchymotic bleedings and edema can develop throughout the body (Greene, 2012; Cullen and Stalker, 2016).

CLINICAL FINDINGS

ICH occurs most common in dogs younger than one year but can occur in unvaccinated dogs of all ages (Green, 2012). The incubation period is two to five days (Cabasso, 1962). In the early phase, a biphasic fever (<40°C) is the first manifestation (Decaro et al., 2008). The clinical course is variable, disease can develop very acutely with death in a few hours after the onset of clinical signs (Cabasso, 1962). In a less acute course, common clinical signs are depression, loss of appetite, increased heart rate, hyperventilation, coughing, vomiting and diarrhea. Although the liver is often severely affected by the disease, icterus is only rarely seen. Tonsillitis and pharyngitis can be severe, cervical lymphadenopathy is frequently present. Because of endothelial damage and DIC, petechial and ecchymotic hemorrhages can occur on mucosae and skin (Decaro et al., 2008; Greene, 2012). Abdominal distention develops because of accumulation of serosanguineous fluid and hepatomegaly. Although rare, some dogs develop neurological signs (ataxia, seizures, coma), which is associated with damage and bleeding of small caliber vessels in the brain (Decaro et al., 2008; Cullen and Stalker, 2016). Neurological signs are more prevalent in foxes explaining the alternative disease name ‘fox encephalitis’ in these animals (Vandevelde et al., 2012). The uncomplicated disease course of ICH takes five to seven days before improvement (Greene, 2012). Keratouveitis with corneal opacity (‘blue eye’) may develop one to three weeks after recovery and results in photophobia, blepharospasm and ocular discharge (Wills, 2000; Decaro et al., 2008).

PATHOLOGICAL FINDINGS

Post mortem lesions in spontaneously fatal acute cases are usually suggestive for a gross diagnosis of ICH. The liver is only slightly enlarged and is turgid and friable with sometimes congestion and mottling (Cullen and Stalker, 2016) (Figure 1A). The wall of the gall bladder is thickened due to edema, which is thought to be a pathognomonic feature (Vandevelde et al., 2012) (Figure 2). Lymph nodes are enlarged, edematous and hemorrhagic. Petechial and ecchymotic bleedings may be present on the serosal surfaces (Figure 3); there is usually a small amount of serosanguineous fluid in the abdomen. Gross lesions in other organs are variable and include mainly hemorrhage. Involved organs are classically brain, lungs, and the bones in younger dogs (Cullen and Stalker, 2016).

Histological lesions in the liver are centrilobular zonal necrosis with scattered deeply acidophilic intranuclear viral inclusion bodies in numerous hepatocytes and Kupffer’s cells (Figures 1B, 1C). Histological lesions in other organs are mainly the result of endothelial damage and DIC consisting of hemorrhage and edema (Cullen and Stalker, 2016). Viral inclusions can also be found in the renal glomeruli and rarely in the tubular epithelium. Focal interstitial nephritis is often present long after the infection (Cullen and Stalker, 2016). Lymph nodes and spleen are reactive and congested with mononuclear cell infiltrates and numerous lymphoid follicles with central necrosis (Greene, 2012).

During convalescence, ocular manifestation may develop, most frequently unilateral. There is diffuse clouding of the cornea (‘blue eye’) with a typical granular aspect due to interstitial edema; conjunctival inflammation is frequently apparent (Willis, 2000). Histological lesions are bilateral although usually of unequal intensity explaining the clinical unilateral manifestation. Histologically, an anterior uveitis is present with lymphocytes and plasma cells surrounding vessels in the iris and ciliary body. There is hydropic degeneration of the corneal endothelium with secondary stromal edema. An intranuclear viral inclusion can rarely be seen. Uncommon complications are interstitial keratitis with fibrosis, synechia posterior and angle obstruction (glaucoma) (Wilcock and Njaa, 2016).

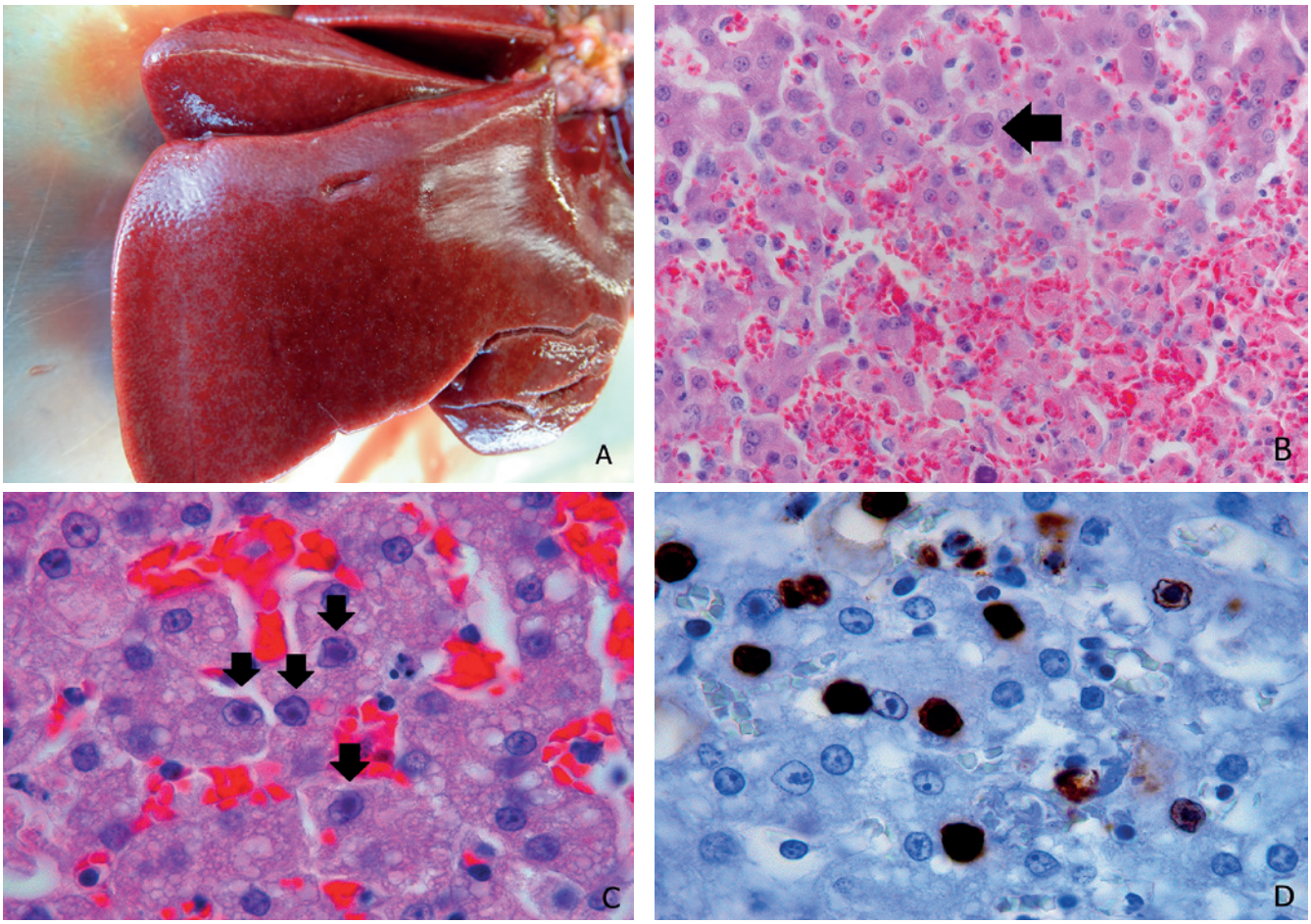


Figure 1. Liver of the dogs in case 1 (A, B) and case 2 (C, D). A. The liver is turgid and friable causing it to rupture easily during post mortal examination. B. Grossly, there is moderate mottling of the parenchyma (A) histologically characterized by necrotizing hepatitis with large, eosinophilic, intranuclear viral inclusions surrounded by a clear halo and marginated chromatin are typical for adenovirus infection (arrows). In case 1, necrosis is prominent at the lower portion of the picture with disruption of hepatic cord architecture, cytoplasmic eosinophilia, karyorrhexis and pooling of blood. HE 400X. C. In case 2, diffuse hepatocytic vacuolar degeneration is characterized by hepatocyte swelling with cytoplasmic vacuolization and numerous inclusions (arrows). D. On immunohistochemistry, numerous hepatocytes and Kupffer's cells stain positive for CAdV, HE 1000X.

DIAGNOSIS, TREATMENT AND PREVENTION

In the early stage, blood examination reveals leukopenia, lymphopenia and neutropenia. Neutrophilia, lymphocytosis, increased alanine transaminase (ALT) and aspartate aminotransferase (AST) develop in a further course (Greene, 2012). Also coagulation abnormalities consistent with DIC are usually apparent during the viremic stage. Ante mortem confirmation is possible through serological testing. Post mortem gross and histological lesions are highly indicative; confirmation can be done by immunohistochemistry, immunofluorescence or polymerase chain reaction (PCR) (Greene, 2012).

Treatment of dogs with ICH is mainly supportive and comprises intravenous fluid therapy, treatment of the DIC, hypoglycemia and reducing endogenic ammonia production (hepatoencephalopathy) (Greene, 2012). Inactivation of the virus occurs at 50-60°C in five minutes, so washing or steaming of textiles at these temperatures is a possibility for disinfection. Chemical disinfection can be done by iodine, phenol and sodium hydroxide (Greene, 2012).

In countries where adequate vaccination is performed by cross-protective CAdV-2 modified live virus, ICH has effectively been controlled and has almost been eliminated from the domestic canine population (Dowgier et al., 2018). A recommended protocol is vaccination at eight to ten and twelve to fourteen weeks with three to four weeks in between. Clinical disease has never been reported in an adult dog with adequate vaccination in puppyhood, but booster vaccination every three years is indicated (Greene, 2012).

CASE DESCRIPTIONS

Case 1

A female Rhodesian Ridgeback of 15 weeks developed lethargia, ventroflexion and partial anorexia.

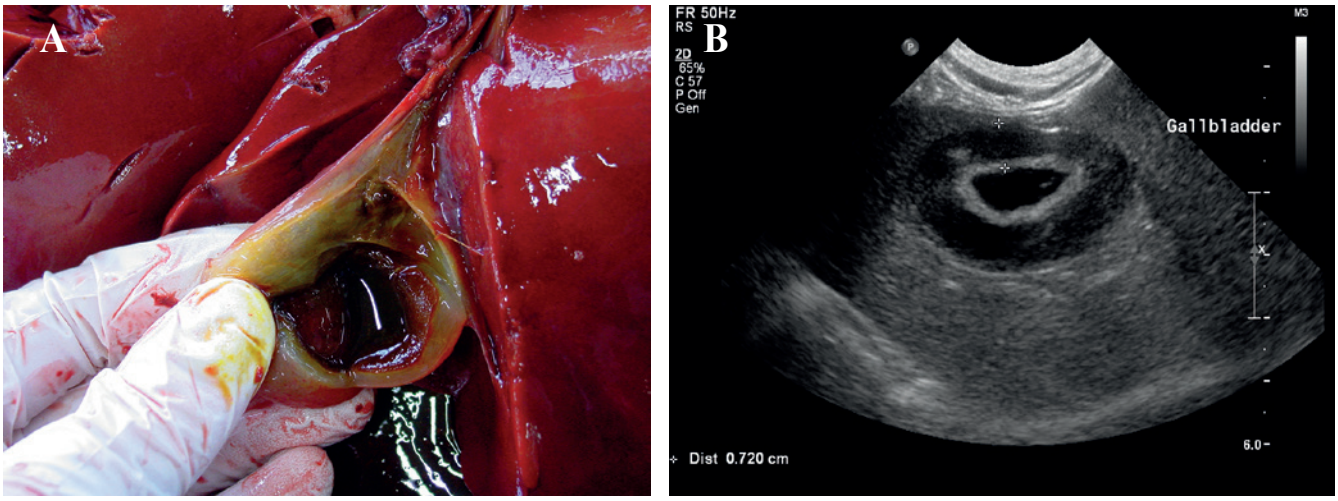


Figure 2. Gall bladder of the dog in case 1. A. Gross examination and B. Transverse section on premortal ultrasound examination. There is marked thickening of the gall bladder wall due to edema. Gall bladder edema is thought to be a pathognomonic lesion of canine infectious hepatitis.

Three days later, the dog was admitted for emergency because of development ataxia and head pressing. Blood examination revealed increased liver enzymes. On ultrasound examination, a generalized abdominal lymphadenopathy, mild hepatomegaly with severely thickened gall bladder and a small amount of peritoneal effusion were noticed (Figure 2). Blood examination revealed a coagulopathy with severe thrombocytopenia (23 K/µL; normal range: 148-484), upper limit prothrombin time (PT) (18s; normal range: 11-17) and markedly increased activated partial thromboplastin time (aPTT) (144s; normal range: 72-102). Finally, cardiac arrest developed, with unsuccessful reanimation. Serological testing for toxoplasmosis, neosporosis, parvovirosis and angiostrongylosis was negative. The clinicians postulated hemorrhagic disorder, infectious or immune mediated encephalitis and metabolic encephalopathy as main differential diagnoses. The owner was a breeder of Rhodesians. The pup belonged to a litter of eleven but only one other pup was present at the moment of the disease. Although they slept and lived together, this other pup did not develop any signs. Vaccination against canine distemper virus and canine parvovirus was performed at eight weeks, vaccination against *Bordetella bronchiseptica* and canine Parainfluenza virus at ten weeks. A rabies vaccine was administered at twelve weeks. The first core vaccination was planned at sixteen weeks of age.

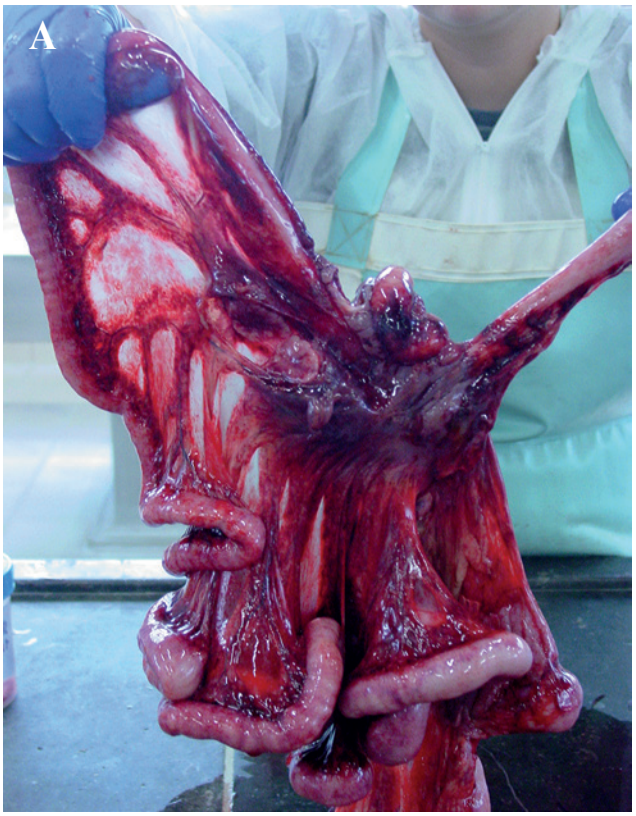
At necropsy, the liver was moderately pale, enlarged and mottled with a scant amount of fibrin strands on the capsule with severe edema of the gall bladder (Figures 1A and 2). There were several superficial ruptures secondary to reanimation causing hemoabdomen. The lymph nodes were severely enlarged and hemorrhagic, the spleen was moderately enlarged with white pulp hyperplasia at cut surface. The mesenteric lymph nodes were edematous and hemorrhagic on cut surface. Extensive petechial and ecchymotic hemorrhages covered the abdominal serosal surfaces (Figure 3). In the brain, dispersed small hemorrhages were bilaterally present in the grey and white matter of the basal nuclei and in the parenchyma of the thalamus (Figure 4).

Histologically, severe multifocal midzonal to centrilobular hepatic necrosis with large eosinophilic intranuclear viral inclusion bodies was present (Figure 1B). The mesenteric lymph nodes were highly reactive with proliferation of lymphoblasts and secondary follicle formation. In the brain, there was presence of disseminated perivascular hemorrhage, most extensive in the basal ganglia and thalamus (Figure 4). Immunohistochemical staining for CAdV revealed numerous positive staining hepatocyten and Kupffer's cells in the liver, fewer positive staining macrophages in the mesenterial lymph node and renal glomeruli (mesangial cells). Also in the brain, several affected bloodvessels showed positive staining endothelial cells.

Case 2

A male Chihuahua of fourteen weeks died within two days after developing high fever with nasal discharge at a small dog breeding facility. Three other pups, one from the same and two from another litter, developed comparable clinical signs in the same week but recovered. The pups are home bread and do not have contact with other dogs than the owner's. The core vaccination is administered at ten weeks of age with repetition at fourteen weeks. The owner introduced a new adult male from Russia seven months prior to the disease manifestation; this dog never showed any clinical signs and was well-vaccinated. The pups are only allowed to go outside on a walled courtyard.

At necropsy, no gross lesions typical of ICH were present. Only an enlarged pale liver and spleen, focal



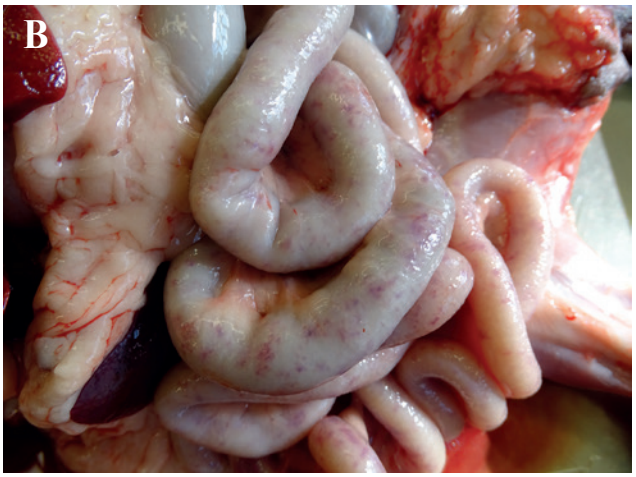


Figure 3. Intestine and mesentery of the dogs in A. case 1 and B. case 3. Both pictures display intestinal serosal hemorrhage, although more extensive and suffusive within the mesentery and mesenteric root of the dog in case 1. Hemorrhagic diathesis is a common sequela of fulminant infection due to DIC and endothelial damage.

renal hemorrhage and melena were the most obvious findings.

At histological examination, there was panlobular vacuolar degeneration of hepatocytes with numerous intranuclear acidophilic inclusions (Figure 1C). Identical inclusions were present in the spleen and kidneys within respectively, macrophages and glomerulic mesangial or endothelial cells. The spleen is highly reactive, displaying hyperplasia of the white pulp with often central necrosis of lymphoid follicles. Immunohistochemical staining of the liver for CAdV highlights numerous positive staining nuclei and fewer positive glomerular mesangial cells in the kidney (Figure 1D).

Case 3

A female Staffordshire Bull Terrier of twelve weeks old developed high fever (40°C) and lethargy. At ultrasound examination, a thickened gall bladder wall with an anechogenic enlarged liver and free abdominal fluid was noticed. The pup died between 24 and 36 hours after hospitalization. The dog had been in the owner's possession for three weeks after buying it at a small breeding facility. One other well-vaccinated adult dog had been with the owner for years. The pup described in this case had only received the first core vaccination at eight weeks of age. A week before the illness, the dog of a friend entered the house and had contact with the pup. This dog did not display any signs of disease at that time.

At necropsy, the liver was moderately enlarged, turgid and friable with a mottled aspect and scattered fibrin deposition at the capsular surface. The gall bladder wall was severely thickened and edematous. There was generalized lymphadenopathy with marked edema and splenomegaly. The small intestine and urine bladder displayed moderate multifocal serosal hemorrhages (Figure 3). The abdominal cavity contained an abundant amount of serosanguineous fluid (200ml). The stomach and duodenum contained a moderate amount of dark brown mucous content (digested blood).

At histological examination of the liver, multifocal midzonal to centrilobular coagulation necrosis with numerous eosinophilic hepatocellular and endothelial intranuclear viral inclusion bodies were present. The spleen and mesenteric lymph node were highly reactive. Immunohistochemical staining for CAdV revealed numerous positive staining hepatocytes and Kupffer's cells in the liver, fewer positive staining macrophages in the mesenterial lymph node and renal glomeruli (mesangial cells). Also in the brain, several bloodvessels showed positive staining endothelial cells, although no histological lesions were present at hematoxylin-eosin staining.

DISCUSSION

ICH is a classical disease in dogs, although it is very rarely encountered by most veterinary practitioners due to widespread vaccination (Balboni et al., 2014; Dowgier et al., 2018). Most veterinarians are not familiar with the clinical or pathological manifestations of this disease, although ICH does occur in Belgium. The patients in the three present cases were admitted

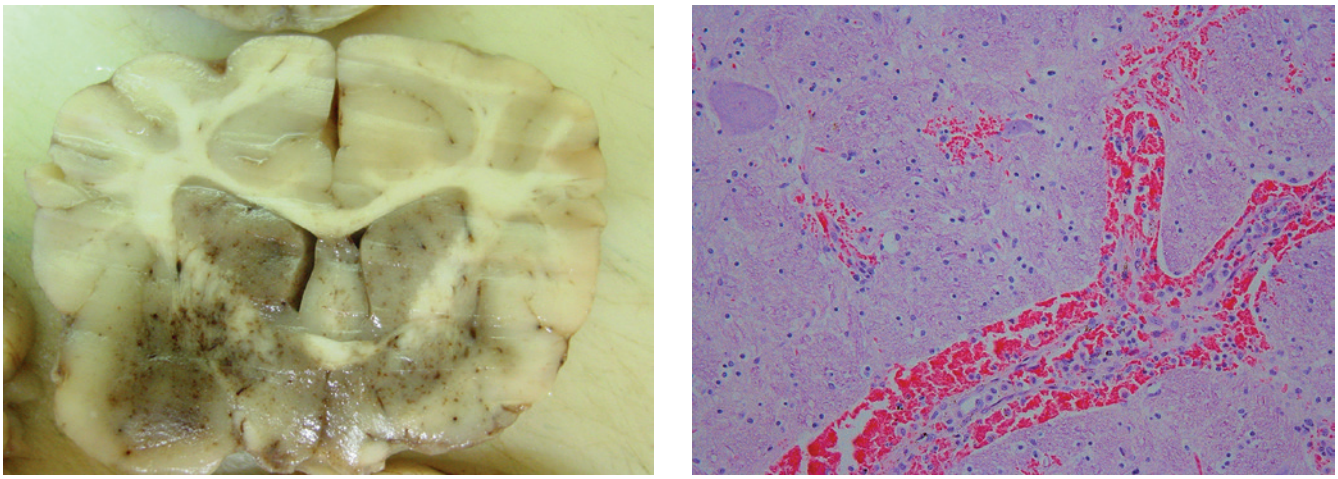


Figure 4. Brain of the dog in case 1. Bilaterally dispersed small hemorrhages in the grey and white matter within the basal nuclei of the cerebrum, gross and histologically. Microvascular bleeding in the brain is a rare development in dogs but a common finding in wild species explaining the more pronounced neurological signs in foxes. In these animals, ICH is called fox encephalitis. HE 200X.

in a period of two months at the necropsy facility of the Faculty of Veterinary Medicine (Ghent University) in 2019. This is remarkable because only four other non-co-occurring ICH cases have been seen at the necropsy facility since 2010; this in comparison to 743 cases of parvovirosis and a total of 3065 necropsied dogs in the same period. A common source of infection for these three cases was however not likely because of a scattered geographical distribution and different origin of the three pups. The source of infection for all three cases could not be traced. However, in one case (2), contact with a foreign adult dog could have been the cause. It was a Russian male dog, which had been introduced seven months earlier. As urinary excretion has been demonstrated in cases of ICH up to nine months post infection (Baker et al., 1954), it could be possible that the Russian dog was still infectious after being infected abroad. Unfortunately, except for correct vaccination according to the owner, no history of the Russian dog was available. In addition, the virus is quiet resistant in the environment increasing the importance of indirect transmission and making it more difficult to track down the source of the infection (Greene, 2012).

The fifteen-week-old Rhodesian Ridgeback in case 1 did not receive its first core vaccination, leaving it vulnerable for infection. The owner believed the combination of the rabies and core vaccination would be too much of a burden for the pup, being the reason for the delay of the core vaccination. Curiously, the only other remaining pup from the same litter was not vaccinated neither; it lived and slept together with the infected pup but did never develop any signs of disease. The fourteen-week-old Chihuahua in case 2 and the twelve-week-old Staffordshire Bull Terrier in case 3 received their first core vaccination but not the booster. A second vaccination is essential for adequate immunity explaining the susceptibility of these dogs once maternal immunity had disappeared (Greene, 2012). The dams in all three cases were well-vaccinated according to the owners. After the diagnosis had been made in case 2, the vaccination protocol was changed from ten and fourteen weeks to nine and twelve weeks. No other cases emerged in the following two litters in the next period of one year.

Another possible source of infection is wild carnivores susceptible to CAdV-1, in Western Europe being mainly foxes and mustelids. In some studies, a CAdV seroprevalence has been indicated in red foxes (*Vulpes vulpes*) of 19% to 64.4% in the UK (Thompson et al., 2010; Walker et al., 2016a), 3,5% in Germany (Truyen et al., 1998), and 59,6% in Scandinavia (Akerstedt et al., 2010). Unfortunately, the serological examinations cannot distinguish CAdV-1 from CAdV-2. However, CAdV 1 infection in foxes has been reported in the UK and Germany (Walker et al., 2016b; Verin et al., 2019). Red foxes are the most prevalent free-ranging species susceptible to ICH in Europe, and due to their intrusive behavior and high population density, they might play a major role in the disease epidemiology (Dowgier et al., 2018). Virus is excreted through urine and feces, so dogs might be attracted by the smell and infect themselves through oronasal contact with these excreta (Balboni et al., 2014). Also in Flanders, this species is common with occurrence in urban areas (Van Den Berge et al., 2013). Stone martens (*Martes foina*) belong to the *Mustelidae,* which are known to be sensitive to CAdV-1 (Greene, 2012). In Flanders, these animals have been recolonized during the past 25 years (Van Den Berge et al., 2012). Although no cases of ICH or seroprevalence in martens have been reported, they should be regarded as a possible source of infection for domestic dogs.

Neurological manifestation of ICH typically occurs in wild species (e.g. foxes) but are rarely encoun-

tered in domesticated dogs (Cabasso, 1962; Hornsey et al., 2019). Nevertheless, case 1 exhibits typical lesions for involvement of the central nervous system as is seen in fox encephalitis (Cabasso, 1962; Vandevelde et al., 2012). So, it is important to keep CAdV-1 in the differential diagnosis when confronted with a young unvaccinated dog with neurological signs.

The pathological lesions are variable in the described cases. At histological examination of the liver in case 2, there was diffuse vacuolar degeneration of hepatocytes with numerous viral inclusions and without the characteristic presence of hepatic necrosis. Most likely, this animal died in an early stage before hepatic necrosis could develop. This is supported by the fact that gall bladder edema was neither present in this case, nor were hemorrhages and lymphadenopathy. In experimental infection, viral inclusions can be histologically detected after three days, reaching its peak at day 4 and declining at day 5 and 6; at day 8 inclusions can only be found occasionally (Cabasso, 1962). This suggests this animal has been infected around four days prior to its death. Hence, it is important for the pathologist and the clinician to keep in mind acute cases might not exhibit the typical lesions. When a veterinarian is encountered with a dog suspected of ICH, it is useful to perform an ultrasound examination of the abdomen. Gall bladder edema in a young dog, especially in combination with fever, hepatomegaly and systemic lymphadenopathy, is diagnostic for ICH (Vandevelde et al., 2012). However, absence of gall bladder edema does not exclude ICH. In two out of the three cases, gall bladder edema was prominent and was noticed during ultrasound examination by the veterinarian.

In conclusion, in this paper, three cases of canine infectious hepatitis are reported in pups of 15, 14 and 12 weeks of age, respectively. As ICH might be a rare disease, it is not extinct, so adequate vaccination is still necessary because of subclinical carriers, environmental resistance of the virus and circulation in wild carnivores. Two out of the three cases manifested extensive gall bladder edema, which is in agreement with the fact gall bladder edema is typical of ICH. This might be useful for the establishment of a clinical diagnosis through ultrasound examination. It is also important to keep CAdV-1 in the differential diagnosis when confronted with a young, unvaccinated dog with neurological signs.

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Uit het verleden

Ondankbare klant

Zoals het hoort in dierenfabels krijgen dieren menselijke trekjes toebedeeld. Ze voeren het woord, oefenen beroepen uit, enz. Zo spelen dieren zelfs dierenarts in een paar fabelgedichten van La Fontaine

We zien, onder meer, hoe een ooievaar een delicate operatie uitvoert bij een gulzige wolf met slokdarmobstructie: een been was er in blijven steken. Met zijn lange bek en hals slaagt hij er in het 'vreemd voorwerp' te verwijderen. Maar dan vraagt de operateur het ereloon. 'Wat? Hoe durf je!', repliceert de wolf: 'ik heb mijn slokdarm teruggetrokken uit jouw hals!'

In een andere fabel van dezelfde La Fontaine prijst een wolf zich aan om dieren te verlossen van hun lijden. Zijn specialiteit is … uiteraard chirurgie.

Fables de La Fontaine. Le loup et la cigogne, door Marc Mammerickx gepresenteerd in La Semaine *Vétérinaire 769, 18 maart 1995*.

Luc Devriese. Met dank aan Paul Tavernier