Clinical communication — Kliniese mededeling

Congenital dilatation of the large and segmental intrahepatic bile ducts (Caroli’s disease) in two Golden retriever littermates

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ABSTRACT

Two, sibling, male Golden retriever puppies, 13 weeks of age, were presented with congenital biliary cysts of the liver involving both hepatic and segmental bile ducts, as well as bilateral polycystic kidney disease. Ultrasonography of the livers of both pups demonstrated segmental cystic lesions that were contiguous with the bile ducts. Histopathology revealed cystic ectatic bile duct hyperplasia and dysplasia with variable portal fibrosis in the liver, while in the kidneys there were radially arranged, cylindrically dilated cysts of the collecting ducts, which extended through the medulla and cortex. This pathology was compatible with that of congenital dilatation of the large and segmental bile ducts (Carolii’s disease) described in humans, dogs and rats. In humans Carolii’s disease has an autosomal recessive inheritance pattern, while in rats activation of the MEK5/ERK cascade initiates the biliary dysgenesis of Carolii’s disease in this species. However, the exact mode of inheritance and pathogenesis of Carolii’s disease in dogs is as yet unknown. Previous reports on congenital hepatic cystic diseases of the dog have described Carolii’s disease like lesions in various breeds, but these are believed to be the 1st reported cases in the Golden retriever breed.

Key words: Carolii’s syndrome, congenital, ductal plate abnormality, Golden retriever, dog, polycystic kidney disease, segmental biliary cysts.


INTRODUCTION

Congenital cystic liver diseases are a complex and confusing group of presumed heritable disorders, in which there is actual or potential cystic dilatation of elements of the bile ducts and are often accompanied by renal lesions, especially cysts of renal tubular origin. These conditions have only recently been classified in the veterinary literature. Although various cystic entities have quite distinct histomorphological features they all appear to represent an anomalous development of intrahepatic bile ducts. Embryological development of the intrahepatic bile ducts is from bipotential liver progenitor cells associated with the primitive mesenchyme around portal veins forming the ductal plate. Remodelling of ductal plates with formation of intrahepatic bile ducts, follows the outgrowth of portal veins from the hilus to liver periphery. Malformation, persistence of, or lack of remodelling of this embryonic double-layered sleeve of cells (ductal plate) results in altered architecture of this system of ducts (ductal plate malformations) and the different levels at which these malformations occur are thought to be linked to the type of disease condition which develops.

Two main groups of congenital intrahepatic bile duct abnormalities have been described in humans namely diseases characterised by atresia of intrahepatic bile ducts, eventually complicated by fibrosis, and those characterised by ectasia of intrahepatic bile ducts with a variable degree of fibrosis (fibrocystic diseases). In the 1st group extrahepatic bile duct atresia and paucity of interlobular bile ducts are recognised. In the 2nd group, autosomal recessive or childhood type of polycystic kidney disease, von Meyenburg complexes are found. Carolii’s disease and congenital hepatic fibrosis are found.

In autosomal recessive or childhood type of polycystic kidney disease malformations of the ductal plate occurs at the level of the interlobular bile ducts, while von Meyenburg complexes (microhamartomas) are ductal plate malformations of embryological vestiges of small interlobular ducts which have failed to undergo involution. Carolii’s disease represents ductal plate abnormalities of the large intrahepatic bile ducts with insufficient resorption of ductal plates resulting in segmental enlargement and ectatic dilatation of primitive bile ducts, which retain communication with the biliary tree. Congenital hepatic fibrosis is thought to arise from ductal plate malformation of interlobular bile ducts, but where there is a concurrent destructive cholangiopathy resulting in scarring fibrosis.

The World Small Animal Veterinary Associations Liver Standardization Group has only recently proposed the nomenclature for the classification of biliary abnormalities in animals. As in humans two main groups are described namely biliary atresia and congenital cystic disease of the liver. Biliary atresia is considered extremely rare in animals and has only been documented in dogs, lambs and calves. Included under congenital cystic diseases are congenital dilatation of the large and segmental bile ducts (Carolii’s disease), juvenile polycystic disease/congenital hepatic fibrosis and adult polycystic disease which includes Von Meyenburg complexes. Among domestic animals congenital hepatic cystic conditions have been documented in all domestic species, with multiple congenital cysts derived from bile ducts being noted in dogs, cats, rats and swine. Congenital cystic diseases of the liver are frequently associated with polycystic kidney disease in all species.

Carolii’s disease is a distinct subgroup of biliary tree anomalies stemming from ductal plate remodelling at the level of the large intrahepatic bile ducts characterised by non-obstructive, segmental, ectatic dilatations of the large intrahepatic bile ducts and often accompanied by diffuse cylindrical dilatation of collecting ducts of the liver.
the kidney. Some authors in the human literature reserve the term Caroli’s disease for those rare cases in which there is only segmental ectatic dilatation of large intrahepatic ducts, whereas the term Caroli’s syndrome is applied to the more common form of the disease, where the bile duct dilatation is accompanied by portal fibrosis, although controversies and overlap of classifications exist.

In the current veterinary nomenclature there is no splitting of these entities with the term Caroli’s disease being applied to conditions characterised by congenital dilatation of the large and segmental bile ducts. In human patients with Caroli’s there is usually biliary stasis that results in biliary lithiasis, cholangitis, cholangiohepatitis, hepatic abscesses and portal hypertension, with onset in childhood. In humans the term Caroli’s disease refers to the liver pathology, although many cases also have concurrent polycystic renal disease characterised by radially arranged, cylindrically dilated cysts of the collecting ducts, which extended through the medulla and cortex. In both dogs and humans the term Caroli’s disease refers to the liver pathology, although many cases also have concurrent polycystic renal disease characterised by radially arranged, cylindrically dilated cysts of the collecting ducts, which extended through the medulla and cortex. In both dogs and humans the term Caroli’s disease refers to the liver pathology, although many cases also have concurrent polycystic renal disease characterised by radially arranged, cylindrically dilated cysts of the collecting ducts, which extended through the medulla and cortex.

In humans there is an association between these congenital cystic liver diseases and inherited polycystic kidney diseases with inheritance patterns placed in 3 basic categories namely autosomal dominant or adult type of polycystic kidney disease (ADPKD), autosomal recessive or childhood type of polycystic kidney disease (ARPKD) and Caroli’s disease with autosomal recessive inheritance, with von Meyenberg complexes being associated with ADPKD, while congenital hepatic fibrosis is linked to ARPKD.

In dogs polycystic hepatic and renal disease resembling ARPKD of childhood have been previously described in young Cairn terriers and West highland white terrier puppies, associated with severe disease in the 1st week of life. A single dog in a series of 7 animals with different types of hepatorenal polycystic disease, reported in 1985, had lesions compatible with Caroli’s disease. A recent report documents a series of 8 young dogs, including 3 Collies, 2 Frisian stabyhouns, 2 Jack Russell terriers and 1 mixed breed dog, with congenital dilatation of the intra- and extrahepatic bile ducts and diffuse cystic kidney disease, consistent with Caroli’s disease described in humans. To the best of the authors’ knowledge this report is believed to be the 1st documenting lesions consistent with congenital dilatation of the large and segmental bile ducts (Caroli’s disease) in the Golden retriever breed.

**CASE HISTORY**

**Clinical history**

Two, male, Golden retriever puppies, 13 weeks of age, originating from the same litter, were presented to 2 separate clinical practices for examination. These 2 animals were emaciated with one weighing only 6.3 kg. Appetite was reported as good and 1 pup was alert and playful, while the other was reported to be quiet and subdued. Abdominal palpation was performed in both cases with lobulated abdominal masses in the region of the kidneys being reported. In-house serum chemistry analysis (Vetscan – Abaxis Model 200-1000) on the depressed dog revealed the following: Urea 8.69 mmol/l (reference range: 2–9 mmol/l) and Creatinine 144 µmol/l (reference range: 27–124 µmol/l).

Cystocentesis was performed on both animals. Urine SGs of 1.008 and 1.010, respectively, were found with a trace of protein, while the urine sediment analyses were unremarkable. Abdominal ultrasound findings in both pups were similar, with small amounts of free fluid noted in the abdominal cavity (ascites). Multiple, small to large, round, irregular cystic spaces were observed throughout the liver in both dogs, and these cysts were observed to be contained within the biliary tree communicating with bile ducts. These segmentally, ectatically dilated cysts, were restricted to the intrahepatic biliary radicles, with no involvement of extrahepatic bile ducts. No evidence of bile duct obstruction was noted. The normal architecture of both kidneys in the two dogs was disturbed with poor cortico-medullary distinction and hyper-echoic areas in the renal medulla. Following these ultrasound examinations, both owners elected euthanasia for the respective puppies.

The veterinarians involved in these cases obtained owners consent to harvest liver and renal tissues for histopathological examination. Gross examination of the livers revealed multiple, segmental, ectatically dilated bile ducts (Fig. 1) while renal pathology was characterised by fine radially arranged cysts, which extend from the medulla through the cortex (Fig. 2). Renal and liver samples for histopathological examination were placed into 10% buffered formalin.

**Histopathology**

Histological examination of liver sections from both pups revealed distortion of hepatic architecture due to cystic ectatic bile duct dilatation. This was associated with portal fibrosis, which extended along the hepatic lobule limiting plate with portal-to-portal linking in some areas (Fig. 3). The dilated bile ducts were lined by columnar epithelium and in some instances contained pink-staining proteinaceous material (Fig. 4). In some areas bulbar infoldings of bile duct epithelium into the luminal space and transductal bridge formation was noted (Fig. 5). Renal histopathology was characterised by radially arranged, cylindrically dilated cysts lined by cuboidal epithelium, which extended through the medulla and cortex (Fig. 6). Interstitial fibrosis was evident between the cystically dilated collecting ducts.

**DISCUSSION**

According to current veterinary nomenclature for morphological characterisation of hepatic pathology, Caroli’s disease of the dog is classified as a congenital dilatation of the large and segmental...
intrahepatic bile ducts\textsuperscript{23}. By contrast, some current human classifications distinguish between Caroli’s disease (simple/classic type) and Caroli’s syndrome (associated with congenital hepatic fibrosis)\textsuperscript{3,6,7,12,17,18,20}. Caroli’s disease is the term used to describe cases in which there is only segmental ectatic dilatation of large intrahepatic ducts, whereas the term Caroli’s syndrome is applied to the more common form of the disease where the bile duct dilatation is accompanied by portal fibrosis\textsuperscript{3,6,7,12,17,18,20}. The degree of portal fibrosis is not used as a criterion for sub-categorisation in the dog and all currently reported cases in this species fall within the category of congenital dilatation of the large and segmental intrahepatic bile ducts identical to Caroli’s disease, as proposed by the World Small Animal Veterinary Associations Liver Standardization Group\textsuperscript{14,15,23,24}. In rats the pathology reported most closely resembles the Caroli’s syndrome with congenital hepatic fibrosis as described in humans\textsuperscript{3,18,19}.

Segmental cystic dilatation of bile ducts due to ductal plate malformation, is central in the pathogenesis of Caroli’s disease and the hepatic histopathology of these pups with bulbar protrusions of the bile duct epithelium into duct lumens, as well as bridge formation across the lumen, are typical of the bile duct dysplasia expected with ductal plate malformations\textsuperscript{3,6,9,19,20}. The renal histopathology of radial cylindrical dilatation of collecting ducts was also consistent with that described in dogs, humans and rats with Caroli’s disease, which is distinctly different to the renal pathology of adult ADPKD in humans, Persian and Persian-cross cats\textsuperscript{3,6,9,19}.

In human patients with Caroli’s there is usually concurrent biliary stasis and this together with the fact that cysts communicate with the rest of the biliary tree, results in varying degrees of acute and chronic ascending cholangitis with periductal fibrosis, biliary lithiasis, cholangiohepatitis, hepatic abscesses and portal hypertension\textsuperscript{6,12,13,17,20,21}. Although no active inflammation was observed histologically in the bile ducts of the pups described in this report, an accumulation of pink-staining proteinaceous material was noted, which raises the level of suspicion for possible biliary stasis in these 2 animals. However, cholangiohepatitis, hepatic abscesses or biliary liths (bile stones) were not observed in this instance or reported in any of the previous documented cases of Caroli’s disease in dogs\textsuperscript{3,6,12,20,21}.

Although considered a rare autosomal recessive inherited disease in humans,
Caroli’s is commonly associated with morbidity related to the complications of choledocholithiasis (common), cholangitis, cholangiohepatitis, hepatic abscessation, bacteraemia, sepsicaemia, pancreatitis resulting from stone passage, portal hypertension and bile duct neoplasia. In those cases with concurrent polycystic renal disease there maybe adverse effects on renal function including reduction in glomerular filtration rates, hypertension and impaired urinary concentration with resultant urinary tract infections, nephritis and eventually end stage renal disease. In most instances clinical symptoms arising from these complications occur in young adults, with the average age of patients at diagnosis being 22 years, although Caroli’s disease can occur in young children and there is a sex predilection for females. Clinical pathological hepatic function tests may or may not be abnormal but are non specific from a diagnostic perspective, with raised alkaline phosphatase levels and bilirubinemia being documented. Although congenital dilatation of bile ducts in dogs is believed to be an inherited condition, the exact mode of inheritance remains undetermined. Unlike humans bile stones have not been documented with Caroli’s disease in dogs and cholangitis in canines is usually mild or not reported. Most cases have been in young dogs of only a few months of age with no sex predilection, animals usually presenting with polyuria/polydipsia, apathy, vomiting and less frequently icterus and ascites. Raised, fasting serum bile acid concentrations and alkaline phosphatase activity in plasma are the most consistent liver function test abnormalities reported in dogs with Caroli’s disease.

While Caroli’s disease represents an in-utero ductal plate abnormality of the large intrahepatic bile ducts in all species, the pathogenesis of this biliary dysgenesis has only been characterised in the rat, where over-expression of extracellular signal-regulated protein kinases in the MEK5/ERK5 cascade have been linked to proliferation of biliary epithelial cells.

Diagnostic imaging techniques of abdominal ultrasonography and radiography are considered the primary diagnostic tools, with demonstration of contiguity between the hepatic cystic lesions and intrahepatic bile ducts being considered paramount in the diagnosis of Caroli’s disease. Other imaging procedures such as nuclear scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI) have also been successfully applied as diagnostic procedures in humans. Histopathology of liver and renal biopsies have high diagnostic specificity when interpreted in conjunction with diagnostic imaging and clinical parameters.

In the two cases described in this report the owners opted for euthanasia and therefore no further follow up on possible progression of the clinical syndrome, pathology or clinical pathology parameters could be made. In humans various treatment modalities are employed including drainage procedures of endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC), sphincterotomy for biliary drainage and bile stone removal, hepatic lobectomy for cases restricted to a single lobe, internal surgical bypass of the biliary tree in diffuse forms of the disease, but ultimately liver transplantation is frequently required. In almost all of the cases of Caroli’s disease reported in dogs the animals have been euthanased at the time of diagnosis and little has been attempted in the way of therapy in this species.

Investigation into the parentage of the pups in this report revealed that this had been the 1st mating between this particular sire and bitch. There were 5 pups in the
REFERENCES


