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Review Article

Surgery Section

Caroli Disease: A Narrative Review of Clinical Spectrum Pathogenesis, Diagnostic Advances, and Management Strategies

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ABSTRACT

Caroli disease is a rare congenital disease of segmental and non obstructive dilatation of intrahepatic bile ducts. This can be simple Caroli disease or Caroli syndrome in combination with congenital hepatic fibrosis and frequent Autosomal Recessive Polycystic Kidney Disease (ARPKD). The symptoms of the patient are usually recurrent cholangitis, hepatomegaly, pruritus, and in serious cases, portal hypertension, bile stones, or Cholangiocarcinoma (CCA). Pathogenesis consists of the development of the malformed ductal plate during embryogenesis, which is often associated with the mutations in PKHD1 gene encoding cholangiocyte cilia and bile duct architecture. Imaging is the most important part of the diagnosis, with the hallmark of the phenomenon of a central dot being identified in the Magnetic Resonance Cholangiopancreatography (MRCP), complemented by ultrasonography, Computed Tomography (CT), Diffusion-Weighted Magnetic Resonance Imaging (DWI-MRI), and genetic testing. The management focuses on complications, antibiotics and biliary drainage in case of cholangitis, segmental resection of the liver in case of localised disease and liver transplant in case of diffuse disease. Multidisciplinary management, that is needed to decrease recurrent infections, review progress in patient and enhance outcomes, should be conducted on a long-term basis.

Keywords: Autosomal recessive polycystic kidney disease, Central dot sign, Cholangiocarcinoma, Hepatic fibrosis, Magnetic resonance cholangiopancreatography

INTRODUCTION

Caroli disease is a rare congenital disease, which involves segmental and non obstructive dilation of the intrahepatic bile ducts [1]. The condition is a fibro Polycystic Liver Disease (PLD) first defined by French gastroenterologist Jacques Caroli in 1958 as the malformation of ductal plates in the embryonic development phase [2]. It is divided into two types mainly: the simple Caroli disease, which is characterised by isolated bile duct dilation and Caroli syndrome, which is complex with congenital hepatic fibrosis and in most cases co-exist with ARPKD [3,4]. Caroli disease is extremely uncommon with the prevalence rate estimated to be around 1 per 1,000,000 individuals [5]. Though the simple form may be diagnosed in adolescence, Caroli syndrome may be seen earlier, as early as the neonatal period [5]. Using new methods in imaging such as MRCP can further help in earlier diagnosis to improve patient outcomes [6]. This narrative review article aimed to present a proper description of Caroli disease, which includes its clinical presentation, pathology, pathogenesis, diagnostic methods, and treatment. It also highlights recent developments in imaging and genetic technology as well as the necessity of long-term surveillance in order to enhance patient outcomes.

DISCUSSION

Clinical Features of Caroli Disease

The characteristic features of Caroli disease are recurrent cases of cholangitis, which manifest as fever, pain in the right upper quadrant of abdomen, and jaundice [7]. These episodes usually arise because of the biliary stasis and the development of intrahepatic calculi [7]. Pruritus and hepatomegaly may also be experienced by patients [7]. The Caroli disease in certain instances is related to the congenital hepatic fibrosis, which causes portal hypertension and splenomegaly [8,9]. In rare cases, the disease may progress to CCA which has the following symptoms like weight loss, abdominal mass or ascites [10]. Few patients may present with gastrointestinal bleeding because of oesophageal varices, which are as a result of portal hypertension [8]. Moreover, Caroli disease may be co-morbid with conditions such as Banti syndrome that is characterised by persistent splenomegaly resulting as pancytopaenia [11]. Clinical features and symptomatology of Caroli disease is mentioned in [Table/Fig-1] [7-11].

Clinical features	Description
Recurrent cholangitis	Presents as fever, right upper quadrant abdominal pain, and jaundice [7],
Underlying cause	Episodes occur due to biliary stasis and formation of intrahepatic calculi [7],
Pruritus and hepatomegaly	Patients may develop itching and hepatomegaly [7].
Association with congenital hepatic fibrosis	Leads to portal hypertension and splenomegaly [8,9].
Progression to Cholangiocarcinoma (CCA)	Rare; symptoms include weight loss, abdominal mass, or ascites [10].
Gastrointestinal bleeding	May result from oesophageal varices secondary to portal hypertension [8].
Co-morbidity with Banti syndrome	Persistent splenomegaly causing pancytopaenia [11].

[Table/Fig-1]: Clinical features and symptomatology of Caroli Disease [7-11].

Age-related Variability in Clinical Presentation of Caroli Disease

Age at presentation in Caroli disease usually influences clinical phenotype, disease trajectory as well as associated co-morbidities. In paediatric age group population (infancy, early childhood), Caroli disease usually presents being a part of the Caroli syndrome spectrum rather than as an isolated ductal abnormality [12]. Children frequently manifest having features related to congenital hepatic fibrosis,

inclusive of early-onset portal hypertension, splenomegaly, growth retardation, hypersplenism, sometimes it also precede overt biliary symptoms [12,13]. Neonates, young children can further atypically present with failure to thrive, recurrent febrile illnesses of unclear origin, or few complications which are related to associated ductal plate malformations [14]. Biliary symptoms in children are subtle or delayed in most of the cases resulting into under-recognition until complications of portal hypertension or recurrent infections prompt imaging-based diagnosis [14].

In contrast, adolescents and adults more usually present having complications directly attributable to long-standing biliary ectasia and stasis [1]. Adult-onset disease is characterised by recurrent infectious and lithogenic complications having a longer subclinical phase, preceding diagnosis [12,15]. Adults have higher chances of developing secondary hepatobiliary sequelae inclusive of segmental biliary cirrhosis, also rarely, malignant transformation over time thus reflecting cumulative epithelial injury, chronic inflammation [12]. Importantly, Isolated Caroli disease without significant fibrosis is more often identified in adulthood cases, whereas syndromic forms are said to be predominate in childhood which thereby underscores a developmental continuum rather than distinct disease entities [12,14].

Additionally, extrahepatic associations also show variability which is related to age. Renal involvements such as medullary sponge kidney or ARPKD are usually found in paediatric age group because of shared embryological origins [16]. Adults can also present later having renal insufficiency, incidental imaging findings [16]. Overall, age at presentation not only differs symptomatology but it also reflects underlying pathogenic mechanisms along with early-onset disease indicating a more diffuse developmental disorder as well as later presentation suggesting progressive biliary pathology evolving over decades [12,14,16].

Impact of Caroli Disease on Health-related Quality of Life (QoL)

Caroli disease is associated with producing substantial negative impact on Quality of Life (QoL), which is largely driven by its chronic, relapsing course as well as multisystem complications [17]. Recurrent episodes of cholangitis further necessitate repeated hospitalisations of patient, long-term antibiotic usage, also frequent imaging contributes to physical exhaustion, psychological stress along with social disruption [17,18]. Persistent symptoms inclusive of pruritus, abdominal discomfort, fatigue impair daily functioning, sleep quality, while portal hypertension- related complications (such as hypersplenism, variceal bleeding) further results in restriction of physical activity, occupational productivity [17]. In patients having Caroli syndrome, growth impairment in childhood age, long-term morbidity from congenital hepatic fibrosis adversely affects educational attainment as well as psychosocial development [9,19]. The need for lifelong surveillance because of increased risk of CCA further imposes an additional psychological burden on patient which is characterised by anxiety, reduced health-related QoL [19]. Caroli disease severity, frequency of infectious complications also associated hepatic, renal co-morbidities are known to be the key determinants of diminished QoL along with partial improvement which is observed only after definitive interventions like liver resection, transplantation in selected patients [19].

Types and Classification of Caroli Disease

The main characteristic of simple Caroli disease is the ductal dilatation with no hepatic fibrosis [20]. On the other hand, Caroli syndrome or complex Caroli disease includes not only the ductal dilation but also congenital hepatic fibrosis, which brings in consequences such as portal hypertension [20]. In addition to this dichotomy, other authors divide Caroli disease according to the extent of involvement: the dilatation can be localised (monolobar, the disease affects one lobe), or diffuse (affecting more than one lobes or the entire liver) [1,21]. Wang ZX et al., categorising 30 patients into Type I (so-called simple Caroli disease) and Type II (with fibrosis), discovered that some clinical and laboratory results (including age of onset, cytopenia) were different in the two types [12].

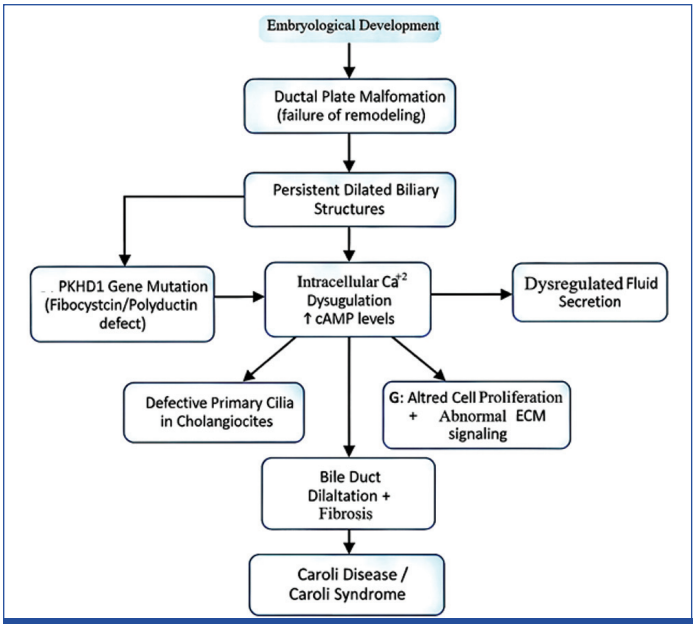
Histopathological Features of Caroli Disease and Caroli Syndrome

In Caroli disease, the dilated ducts are microscopically characterised by thinning of the duct wall, abnormal lumen structure, intraluminal protrusions (bulbar or papillary) of ductal epithelium and periductal inflammation [22]. Recurrent cholangitis may result in reactive changes in the ductal epithelium, neutrophil infiltration, and abscesses in some cases, and fibrosis [22]. Such histologic changes are indicative of chronic injury because of biliary stasis along with presence of infection [22]. The histopathology in Caroli syndrome depicts other additional features of remodelling of hepatic parenchymal [23]. Periportal fibrosis is prominent with thick fibrous bands that run between portal tracts which are often nodular in appearance [23]. The portal vein branches are either hypoplastic or distorted; portal tracts widening can be considered as associated architectural distortion, proliferation of bile ducts and abnormal branching angles of small portal veins [24].

Pathogenesis and Molecular Basis of Caroli Disease

One of the essential characteristics in pathogenesis of Caroli disease is the malformation of the ductal plate at the stage of embryologic development [25]. The ductal plate is temporary embryonic plate which is made up of primitive type biliary epithelial cells (cholangiocytes) surrounding portal tracts; the ductal plate usually differentiates into interlobular bile ducts [25]. In Caroli disease this remodelling did not occur in localised segments resulting in the persistent dilated biliary structures [25]. The most important gene involved at the molecular level is PKHD1 gene, which encodes Fibrocystin/Polyductin (FPC), a protein found at the primary cilia of cholangiocytes, as well as in the basal membrane [1,26]. PKHD1 mutations are traditionally linked to ARPKD, and a renal involvement is also common in Caroli syndrome patients, which is indicative of the widespread molecular defect [26,27]. It has been demonstrated in studies with the PCK rat model (ortholog of ARPKD/Caroli disease) that fibrocystin defects cause defective structure or signalling of cholangiocyte primary cilia [28]. This subsequently leads to the intracellular Ca^{2+} dysregulation, cAMP rise, cell proliferation disruption, abnormal extracellular matrix communications, and fluid secretion dysregulation - all of which contribute to the bile duct dilatation and fibrosis [28]. Recent cases of atypical Caroli syndrome verified by whole exome sequencing showed that the patient had compound heterozygous PKHD1 mutations, which were correlated with histopathologic evidence of malformation of the bile duct, hyperplasia of cholangiocytes, and fibrosis of portal tracts, which is consistent with the molecular-pathologic paradigm [29,30]. Pathogenesis of Caroli disease is presented through flowchart [Table/Fig-2].

Caroli disease is understood as a developmental cholangiopathy within the spectrum of fibro PLD which arises from abnormal remodelling of embryonic ductal plate as well as it is compounded by molecular defects affecting cholangiocyte ciliary signalling [31]. Beyond structural persistence of malformed large intrahepatic bile ducts, experimental as well as review-based evidence shows that defective FPC-mediated ciliary function causes disruption of mechanosensory regulation of intracellular calcium, cyclic AMP pathways, thereby resulting into cholangiocyte hyperproliferation, altered fluid secretion, and progressive bile duct dilatation along with portal fibrosis [26,32]. Insights from PCK rat model, an orthologous model of human Caroli disease, ARPKD, have been very important in showing how ciliary dysfunction drives



[Table/Fig-2]: Pathogenesis of Caroli disease.

biliary cystogenesis and fibrogenesis [28]. Human genetic studies, case reports which are done using targeted sequencing as well as whole-exome sequencing further corroborate this mechanism, thus consistently identifying pathogenic, compound heterozygous PKHD1 variants which are associated with variable hepatic-hepatorenal phenotypes, alongside histopathological findings of dilated bile ducts, cholangiocyte hyperplasia, portal tract fibrosis [27,30,33]. Collectively, all these data supports a unified pathogenetic model in which embryologic ductal plate dysgenesis that is driven by PKHD1-related cholangiociliopathy, initiates a cascade of molecular-structural abnormalities which finally culminate in characteristic biliary dilatation as well as clinical manifestations of Caroli disease [33].

Diagnostic Approaches in Caroli Disease

A diagnosis of Caroli disease is mainly based on imaging, of which the most successful is MRCP [1,34]. The characteristic "central dot sign" that can be observed with MRCP is that of a central dot or bundle of strong contrast enhancement in the dilated intrahepatic ducts and is particular of Caroli disease [34,35]. Also, MRCP has been shown to determine related complications like intrahepatic calculi, hepatic abscess, and portal hypertension [34]. The diagnostic process also uses ultrasonography and Computed Tomography (CT). In ultrasonography, several cystic lesions can be observed in the liver, and in CT, the imaging provides cross-sectional views in order to detect the dilated bile ducts and liver pathology [32]. In other older studies, hepatobiliary scintigraphy with Tc-99m mebrofenin has been used to establish contact between cystic lesions and biliary tree, and this has helped in the diagnosis of Caroli syndrome with congenital hepatic fibrosis [36].

Although MRCP is one of the important aspects in the diagnosis of Caroli disease, diffusion-weighted MRI (DWI-MRI) has shown promise as a complementary technique for evaluating hepatic tissue microstructure [37]. DWI-MRI has been promising in characterising tissue properties and may help detect subtle liver parenchymal changes that are not readily apparent on conventional imaging, thereby providing additional information in the assessment of hepatobiliary disorders [37]. Genetic analysis combined with imaging studies makes it more definitively diagnosed and can guide the management strategy which may involve genetic counselling of the affected families [26]. These developments highlight the role of a multidisciplinary approach of the diagnosis and treatment of Caroli disease to increase the outcomes of patients by promptly and precisely detecting the disease [26]. Diagnostic modalities and their key features in Caroli disease are described in [Table/Fig-3] [26,32,34-37].

Modality	Key findings/ features	Advantages	Limitations/ notes
Magnetic Resonance Cholangiopan-creatography (MRCP) [34]	Characteristic "central dot sign" (enhancing portal radicle within dilated intrahepatic ducts); detects complications such as intrahepatic calculi, hepatic abscess, portal hypertension	Non-invasive, high diagnostic accuracy, best modality for biliary tract evaluation	May not always differentiate from other cystic liver diseases
Ultrasonography (USG) [32]	Multiple cystic lesions in liver	Widely available, inexpensive, non-invasive	Operator-dependent, less specific than MRCP
Computed Tomography (CT) [32,35]	Cross-sectional view showing dilated bile ducts and associated liver pathology	Provides anatomical detail, useful for surgical planning	Radiation exposure, contrast risk
Hepatobiliary Scintigraphy (Tc-99m Mebrofenin) [36]	Demonstrates communication between cystic lesions and biliary tree; useful in diagnosing Caroli syndrome with congenital hepatic fibrosis	Functional assessment of biliary tract	Less commonly used today; limited availability
Diffusion-Weighted MRI (DWI-MRI) [37]	Characterises hepatic tissue microstructure; detects subtle liver parenchymal changes	Provides additional information on tissue characteristics; complements conventional MRI and MRCP	Emerging technique, limited availability and experience
Genetic Testing [26]	Detects mutations (e.g., PKHD1); confirms diagnosis and familial involvement	Definitive diagnosis, guides genetic counselling and prognosis	Requires specialised facilities; not first-line

[Table/Fig-3]: Diagnostic modalities and their key features in Caroli Disease [26,32,34-37].
MRCP: Magnetic Resonance Cholangiopancreatography; USG: Ultrasonography; CT: Computed tomography; Tc-99m: Technetium-99m; MRI: Magnetic resonance imaging; DWI: Diffusion-weighted imaging

Differentiation of Caroli Disease from Mimicking Hepatobiliary Disorders

Caroli disease must be differentiated carefully from several hepatobiliary disorders because its management, prognosis as well as surveillance strategies differ substantially [34]. The main aspect into differentiation lies in showing true communication of cystic, saccular dilatations along with intrahepatic biliary tree which further reflects its origin from ductal plate malformation, a feature which is absent in most mimickers [34]. PLD is most common differential diagnoses although it presents having multiple hepatic cysts, these cysts are epithelial-lined, isolated from the biliary system thus showing no contrast filling on cholangiographic imaging [38]. MRCP is used reliably for distinguishing PLD by absence of biliary communication as well as frequent association with autosomal dominant polycystic kidney disease which is not a defining feature of isolated Caroli disease [1,38].

Choledochal cysts, usually Todani type IVa, closely resembles to Caroli disease because of combined intrahepatic, extrahepatic ductal dilatation [39]. However, Caroli disease is mainly differentiated by its segmental or diffuse saccular dilatation which is limited to intrahepatic ducts, preservation of extrahepatic ducts, as well as presence of the central dot sign thereby representing portal vein radicles within dilated ducts [39,40]. Choledochal cysts usually present earlier in life thus have a higher risk of pancreatobiliary maljunction, as well as it lacks characteristic intrahepatic vascular structures which are seen in Caroli disease [39,40]. Primary Sclerosing Cholangitis (PSC) is

known to be another important differential diagnosis, usually in adults presenting with cholestasis and recurrent cholangitis [41]. PSC shows multifocal short-segment strictures alternating with normal-mildly dilated ducts, thus creating a classic "beaded" appearance which can be adequately seen on MRCP [41]. In addition, PSC is associated with inflammatory bowel disease as well as shows progressive fibrosing obliteration of bile ducts rather than being a congenital ductal dilatation [41]. Histopathological studies describe concentric periductal fibrosis ("onion-skinning") which is typically seen in PSC, which thereby contrasts with non obstructive, ectatic bile ducts of Caroli disease [9,41].

Recurrent Pyogenic Cholangitis (RPC) must be differentiated from Caroli disease, especially in Asia region population [42]. RPC which is usually characterised by intrahepatic pigment stone formation, biliary strictures, as well as lobar atrophy, all of which are secondary inflammatory changes rather than congenital anomalies [42]. Imaging studies stress that RPC usually lacks the uniform saccular ductal dilatation, central dot sign which is typically observed in case of Caroli disease, also patients often have a history of repeated bacterial infections and parasitic infestations [2,42]. Biliary hamartomas (von Meyenburg complexes) can further mimic Caroli disease because of their multiple cystic appearance; however, they are very small in size (<15 mm), non communicating lesions which are derived from embryologic ductal plate remnants [43]. Advanced MR imaging along with pathological correlation shows that these lesions do not fill with contrast on MRCP, usually these are incidental findings without cholangitis, biliary stones, which are hallmark complications of Caroli disease [4,43].

Finally, Caroli syndrome must be differentiated from isolated type of Caroli disease by presence of congenital hepatic fibrosis and portal hypertension, which is often accompanied by splenomegaly and varices [24]. Both share ductal ectasia although Caroli syndrome represents a broader type of fibropolycystic disease spectrum having worse long-term outcomes [24,32]. Comparative features of Caroli disease and its differential diagnoses are described in [Table/Fig-4] [1,2,4,9,32,34,38,40-43].

Risk of Malignancy, Disease-Related Morbidity, and Mortality in Caroli Disease

Caroli disease is known to be a rare congenital dilatation of the intrahepatic bile ducts, and its fibrotic variant named as Caroli syndrome carry a significantly elevated risk of malignant transformation which is most notably intrahepatic CCA [20]. The incidence of CCA among patients having CD/CS varies widely across cohorts but it averages approximately 6-7% with some reports ranging from about 2.7% to above 30% in smaller case series [10,20]. This risk is substantially very higher than in the general population, with some of the published literature estimating up to a 100-fold increase in CCA risk in affected individuals because of prolonged biliary stasis as well as chronic inflammation [15]. Importantly, malignant lesions are usually detected incidentally in surgical specimens rather than preoperatively thus reflecting diagnostic challenges thereby it underscores need for adequate long-term surveillance [20].

Morbidity and mortality in Caroli disease is usually associated with recurrent biliary complications, progressive hepatic dysfunction [15]. Repeated episodes of cholangitis, biliary lithiasis as well as abscess formation further contributes to significant disability, repeated hospitalisations, along with declining Quality of Life (QoL) [15]. In cohorts who are undergoing surgical intervention, postoperative complications, disease recurrence remain notable also mortality associated with untreated, advanced disease can be high [15,19]. In patients selected for liver resection and transplantation, perioperative outcomes can be acceptable with early intervention; however, overall survival figures also vary, and recurrence of cancer or liver failure contributes to reduced of long-term survival in some of the cases of Caroli disease [17,19]. Moreover, in large retrospective analyses of liver transplantation for CS, 1, 3, and 5-year survival rates were documented at approximately 90%, 85%, and 78.5%, respectively thereby indicating that definitive surgical therapy can help further to improve prognosis in few selected patients [19].

Management and long-term surveillance of Caroli Disease

Caroli disease is managed medically wherein the first phase is to treat the most common complication and the one which could be fatal; bacterial cholangitis [18]. The initial line treatment is consistent with acute cholangitis general treatment: haemodynamic support, broad-spectrum antibiotics as soon as possible, based on the presence or absence of obstruction or sepsis, and early decompression of the biliary (endoscopic, percutaneous or surgical) is needed [18].

Condition	Key features	Imaging characteristics	Clinical associations/Age of onset	Differentiating points	References
Caroli Disease (Isolated Type)	Segmental or diffuse saccular dilatation of intrahepatic bile ducts	MRCP: saccular intrahepatic ductal dilatation with central dot sign (portal vein radicles within dilated ducts)	Can present at any age; recurrent cholangitis, intrahepatic stones	True communication with biliary tree; absence of extrahepatic duct involvement; hallmark central dot sign	[1,34]
Caroli Syndrome	Caroli disease + congenital hepatic fibrosis	Saccular intrahepatic ductal dilatation with fibrosis; portal hypertension features	Often presents with splenomegaly, varices, portal hypertension	Fibrosis and portal hypertension distinguish it from isolated Caroli disease; worse long-term prognosis	[24,32]
Polycystic Liver Disease (PLD)	Multiple hepatic cysts, epithelial-lined	Cysts isolated from biliary tree; no contrast filling on MRCP	Often associated with autosomal dominant polycystic kidney disease	No biliary communication; lacks central dot sign; systemic cystic involvement	[1,38]
Choledochal Cyst (Todani Type IVa)	Combined intra- and extrahepatic ductal dilatation	MRCP shows both intra- and extrahepatic duct involvement; lacks central dot sign	Usually presents in childhood; may have pancreatobiliary maljunction	Extrahepatic duct involvement; absence of central dot sign; earlier age of onset	[39,40]
Primary Sclerosing Cholangitis (PSC)	Chronic inflammatory fibrosis of bile ducts	Multifocal short-segment strictures alternating with normal/mildly dilated ducts ("beaded" appearance)	Adults; often associated with inflammatory bowel disease	Progressive fibrosing obliteration vs congenital saccular dilatation; "onion-skin" periductal fibrosis; central dot sign absent	[9,41]
Recurrent Pyogenic Cholangitis (RPC)	Intrahepatic pigment stones, biliary strictures, lobar atrophy	Irregular intrahepatic ducts; lacks uniform saccular dilatation	Common in Asia; history of repeated bacterial/parasitic infections	Secondary inflammatory changes vs congenital ductal plate malformation; central dot sign absent; stones common	[2,42]
Biliary Hamartomas (von Meyenburg Complexes)	Multiple small (<15 mm) cystic lesions	Non communicating cysts; no contrast filling on MRCP	Usually incidental; asymptomatic	Small size; no biliary communication; lack of cholangitis or stones	[4,43]

[Table/Fig-4]: Comparative features of Caroli disease and its differential diagnoses [1,2,4,9,32,34,38,40-43].

The current literature on guidelines and reviews supports the use of short courses of antibiotics after successful drainage (47 days in the majority of the cases with drainage achieved), and extended or personalised treatment is used when drainage is delayed or the organisms/clinical course justify it [18,44].

In clinical practice, although antibiotic protocols which are specific to Caroli disease are not available, empirical therapy is recommended for cholangitis should cover common biliary pathogens which are inclusive of *Escherichia coli*, *Klebsiella spp.*, *Enterococcus spp.* As well as anaerobic organisms in severe infection [45]. Frequently regimens taken into usage are third-generation cephalosporins, piperacillin-tazobactam, fluoroquinolones, or carbapenems in cases of septic shock or suspected multidrug-resistant organisms [14,45]. Blood, bile cultures are strongly recommended for guiding de-escalation once sensitivities are available usually in case of patients having recurrent cholangitis who are prone to resistant flora [45,46]. Adjunctive use of ursodeoxycholic acid has been shown to improve bile flow as well as reduce intrahepatic stone formation thereby plays an important role in decreasing recurrent infectious episodes, although it does not alter the underlying ductal malformation [47].

The ultimate treatment is dependent on the anatomic disease spread and presence of hepatic fibrosis [48]. In the case of the Caroli disease that is truly localised (unilobar or segmental), formal hepatic resection is the most desirable choice as it removes the dilated biliary segments, decreases the recurring cholangitis and removes the nidus of stone formation or malignant transformation [15,49]. In comparison, diffuse Caroli disease (particularly in the presence of congenital hepatic fibrosis, i.e., Caroli syndrome) is only infrequently amenable to resection and best treated using orthotopic liver transplantation, which has an excellent long-term survival of well-selected patients [50]. In several surgical series and the comparative reviews, low rates of perioperative mortality and favourable results are reported in cases where resection or transplantation is performed depending on extent of disease [48].

Endoscopic, percutaneous interventions are very important which plays complementary role in both acute-chronic management of Caroli Disease [51]. ERCP further allows biliary decompression, extraction of intrahepatic stones, dilation of strictures, as well as placement of stent [45,51]. ERCP has also shown reduction into frequency, severity of recurrent cholangitis episodes usually in patients having segmental biliary obstruction [18,51]. Cholangioscopy-guided lithotripsy is very useful for complex intrahepatic calculi in selected patients of Caroli disease [52]. When endoscopic access is not feasible to be performed, percutaneous transhepatic biliary drainage proves as an effective alternative in unstable patients or as a bridge to definitive surgical as well as transplant management [18,34].

In addition to infectious complications, management approaches must focus on addressing hepatolithiasis, secondary biliary cirrhosis, portal hypertension, hypersplenism as well as nutritional deficiencies through structured surveillance, also endoscopic therapy for varices when it is required, correction of metabolic abnormalities, timely escalation to surgical and transplant intervention in progressive type of Caroli disease [20,34,53]. Persistent and recurrent complications despite of optimal medical, interventional therapy further warrants an early multidisciplinary reassessment [15,18].

The fact that Caroli disease has a higher lifetime risk of intrahepatic CCA and recurrent biliary sepsis makes the long-term follow-up and surveillance following the conservative or definitive treatment of the disease significant [15,20]. The approach to surveillance differs according to the healthcare centre, although as a rule it involves clinical examination, liver imaging and timely investigation of new or recurring cholestatic symptoms; early referral to definitive surgical intervention is recommended in case of recurrent infections, stones, progressive liver dysfunction or suspicious lesions [15]. Timing of intervention and outcomes are best in multidisciplinary care (hepatology, interventional endoscopy/radiology, hepatobiliary surgery/transplant teams) [15].

Paediatric-specific Management Considerations in Caroli Disease

Considering paediatric population, Caroli disease requires a distinct, multidisciplinary type of management approach because it usually presents early in life also it is commonly associated with congenital hepatic fibrosis, ARPKD [26,34]. Children often manifest having recurrent episodes of bacterial cholangitis, portal hypertension, hepatosplenomegaly, hypersplenism, growth failure, as well as fat-soluble vitamin deficiencies, which requires close monitoring by paediatric hepatology teams [7,14,31]. Medical management must focus on prompt, aggressive treatment of cholangitis, prevention of biliary stasis-related complications along with ursodeoxycholic acid, nutritional optimisation as well as surveillance for portal hypertension-related sequelae inclusive of variceal bleeding [34]. Endoscopic or percutaneous biliary drainage can be required for controlling recurrent infections, hepatolithiasis, although these interventions are usually considered as temporary approach rather than being curative in diffuse type of disease [51]. Early referral to specialised centers for liver transplant is usually done because the progression of disease in children can be rapid-unpredictable [53]. Liver transplantation is often indicated at a younger age than in adult population which is done usually in those with recurrent, refractory cholangitis, progressive hepatic dysfunction, complications of portal hypertension, and it also offers excellent long-term survival, QoL in carefully selected paediatric patients [53].

Patient Education and Genetic Counselling in Caroli Disease

Patient, genetic counselling forms an integral part of long-term management in cases of Caroli disease, Caroli syndrome, because of their congenital origin, chronic clinical course as well as potential for serious hepatobiliary complications [27]. Counselling aims for education of patients, families about mechanism of disease, expected clinical course, early identification of complications inclusive of recurrent cholangitis, portal hypertension as well as malignancy risk, along with the need for lifelong surveillance, adherence to follow-up protocols, thereby helps in improving self-management, QoL [19,27]. Genetic counselling is known to be particularly relevant because Caroli disease, especially when it is associated with congenital hepatic fibrosis, is most usually linked to autosomal recessive inheritance, usually it includes PKHD1 mutations, and it can also coexist with ARPKD [27,30]. Genetic counselling is known to be very helpful to clarify inheritance patterns, recurrence risks (which includes 25% risk in future offspring of carrier parents) as well as implications for siblings, family members [30,54]. Genetic counselling helps guiding decisions in consideration of genetic testing, family screening, family planning [30,54]. Overall, integrated patient, genetic counselling provides significant benefits by enhancing disease understanding, enabling informed type of decision-making, facilitating early identification of relatives who are at-risk also supporting a multidisciplinary, preventive approach to care [54].

CONCLUSION(S)

Caroli disease is a rare congenital disorder that manifests itself through non obstructive, intrahepatic bile duct dilatation, which can be complex due to cholangitis, portal hypertension or CCA. The recent developments with regard to imaging especially MRCP coupled with genetic test have enhanced early diagnosis

and characterisation. The treatment of management depends on individual approaches, which can be antibiotics and biliary debridement, or hepatic resection or liver transplant in severe cases. As it is a chronic condition with a high risk of complications and the association with congenital hepatic fibrosis and ARPKD, multidisciplinary care and continuous monitoring is the key to the best patient outcomes and the possibility of better prognosis.

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