Pediatric Surgery International (2019) 35:273–282
https://doi.org/10.1007/s00383-018-4392-4

REVIEW ARTICLE

Choledochal malformations: global research, scientific advances and key controversies

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Accepted: 23 October 2018 / Published online: 7 November 2018

Abstract

Choledochal malformations (CMs) represent a spectrum of relatively rare and complex congenital anomalies, characterized by abnormal dilatation of the biliary tract in the absence of any acute obstruction. Today, almost 20% of CMs can be detected in-utero using maternal ultrasonography. Formal scientometric analysis was used to identify where modern CM research is taking place and perhaps where our attention should be directed in the future. Thus, this article offers a comprehensive review of recent scientific advances relating to CMs including the current understanding of etiology and classification, whilst also discussing key controversies such as risk of malignant transformation and the role of newer modalities of surgical treatment. Although laparoscopic excision of CMs and biliary reconstruction is nowadays feasible and safe, care should be taken before dispensing with standard open techniques, which have minimal complication rates and proven long-term benefit.

Keywords Choledochal cyst · Choledochal malformation · Choledochal diverticulum · Choledochocele · Bile duct · Biliary tract

Introduction

Choledochal malformations (CMs) represent a spectrum of relatively rare complex congenital anomalies, which may be characterized as an abnormal dilatation of the biliary tract (i.e., outside and/or inside of the liver) in the absence of any acute obstruction.

The first description of a classical choledochal cyst replacing the common bile duct was by the German anatomist Abraham Vater in 1723 during a post-mortem dissection in Heidelberg [1] (Box 1). Since then, a plethora of CMs have been described in the literature and the challenge has been on how to bring order and logic to their classification and surgical treatment. The aim of this review is to summarize the current state of CM knowledge using formal scientometric analysis to identify where modern research is taking place, whilst also highlighting areas of controversy and perhaps where our attention should be directed in the future.

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Box 1 Historical aspects of CMs

1723	First description of a choledochal cyst by Abraham Vater (Germany)
1852	First detailed report of clinical features and external drainage of choledochal cyst in a 17-year-old girl by Halliday Douglas (Scotland)
1895	First operative intervention with creation of internal fistula with adjacent jejunal loop using a Murphy's button by William Swain (England)
1924	First successful operation involving excision of choledochal cyst and restoration of continuity using a hepaticoduodenostomy by Golder Lewis McWhorter (USA)

1995	First successful laparoscopic excision of a choledochal cyst and Roux loop reconstruction in a 6-year-old child by Gianantonio Farello (Italy)

Materials and methods

Literature-based search

To identify as many publications as possible relating to CM research, a systematic literature-based search was performed using the Web of Science™ database (Clarivate Analytics, Boston, USA) [2]. This online subscription-based research platform, which provides temporal coverage from the year 1900 onwards, was accessed on 30 September 2018. A combination of the following linked search terms were used, taking into account the varied nomenclature for CMs: "*choledoch* malformation**" OR "*choledoch* cyst**" OR "*congenital* bil* duct* cyst**" OR "*choledochocele**" OR "*congenital* choledoch* divertic**". A "title" rather than a "topic" search approach was applied to determine only the most appropriate research items. No language restrictions were imposed. As the inclusion of various parameters into the database requires a certain time, results from 2018 were excluded from the search to avoid incomplete data acquisition but scientific articles published in 2018 were certainly considered for "Discussion" section. Any ambiguities during this search process were resolved by consensus of all authors.

Selection criteria and data analysis

The retrieved data on CM-related publications was critically evaluated and categorized with regard to publication date, document type, journal title, subject categories and language. Total research output of countries, institutions and individual authors was determined and systematically analyzed. Qualitative research aspects such as citation rate and *h*-index were assessed as semi-qualitative variables. The *h*-index is a metric, which incorporates a citation index and author or institution productivity, quantifying importance, impact and significance of research contributions [3]. In this study, the *h*-index has also been used to estimate the CM output of publishing countries. Complete bibliographic data was downloaded as plain text files and extracted into an electronic database in a standardized manner. Choropleth mapping (i.e., differences in color values to represent geographical data) and network diagrams were employed to visualize results.

Results

Publication and citation trend

The first scientific article relating to CMs was published in 1902 and the number of subsequent papers increased almost annually, associated with a steady increase in citations (Fig. 1). Until 1960, there was a relatively low publication base, consisting of only 124 articles. Thereafter, there has been a steep increase in the number of published items, with a total of 2463 papers by 31 December 2017 (i.e., 95.0% of all CM publications were published after 1960). Between 1923 and 2017, these articles received a total of 24,559 citations and an average of 255.8 citations per year (range 0–1352).

Global research productivity

The 2463 identified articles on CMs originated from a total of 76 countries (Fig. 2). Asia, Europe and North America were the main sources with little or no contribution by African countries (apart from South Africa). Globally, the largest number of papers relating to CMs was published by the USA [$n=358$; (14.5%)], Japan [$n=286$; (11.6%)] and China [$n=120$; (4.9%)]. Germany [$n=81$; (3.3%)] was the most productive country in Europe, followed by the United Kingdom [$n=66$; (2.7%)] and France [$n=62$; (2.5%)]. Most CM publications were written in English [$n=1{,}934$; (78.5%)], followed by German [$n=122$; (5.0%)] and French [$n=47$; (4.9%)].

Country-specific *h*-index

The USA had the highest country-specific *h*-index in the field of CM research ($h=42$), closely followed by Japan ($h=41$) and then China ($h=21$). European countries were

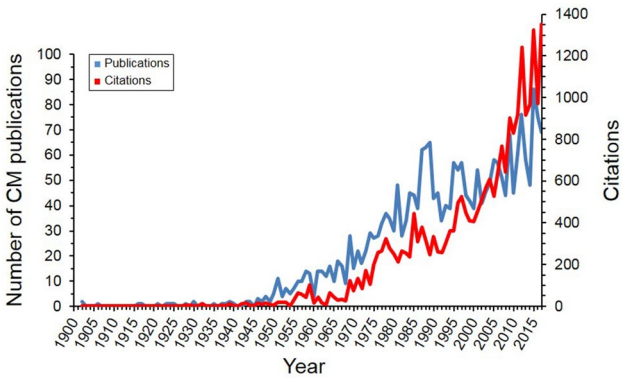

Fig. 1 Overall number of CM publications and received citations in the timespan 1900–2017

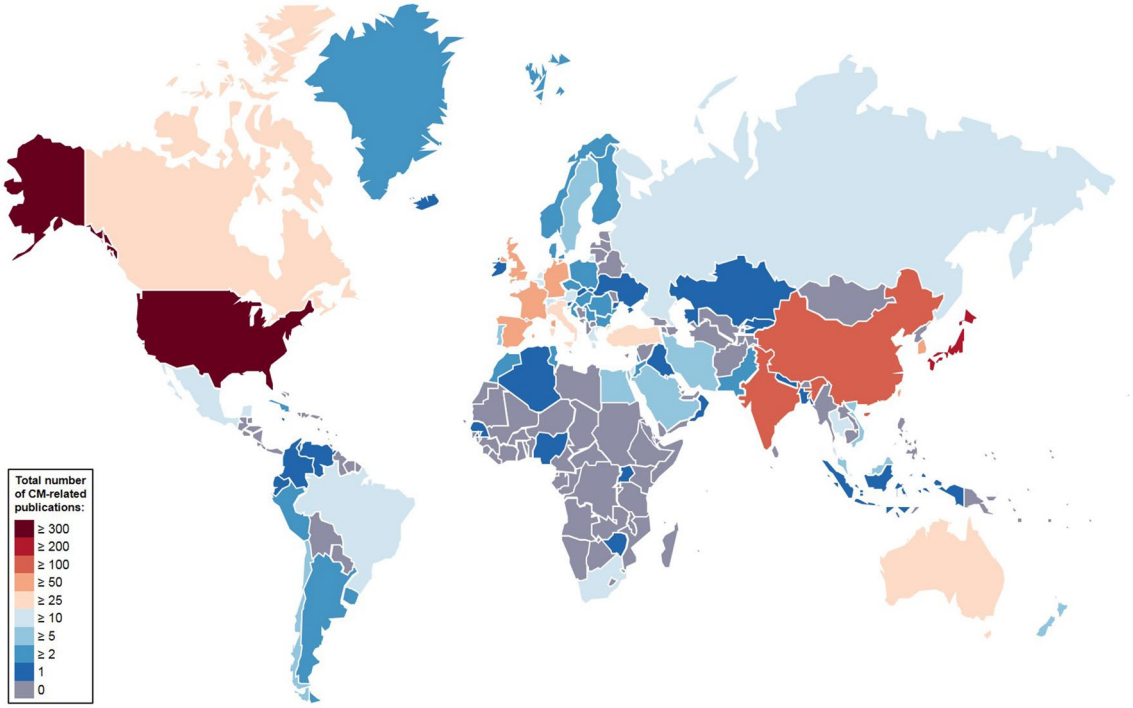

Fig. 2 Choropleth mapping visualizing global publication volume in the field of CM research

lower, e.g. the United Kingdom ($h = 17$), Germany and France (both $h = 9$). In contrast, many of the African, Middle Eastern and Eastern European countries had a country-specific h-index of 1 or 0.

International research collaborations

Researchers in 30 (39.5%) of the identified 76 countries that published CM-related work were involved in international research collaborations (Fig. 3). Australia, China, and the USA combined the highest number of cooperation articles with authors from other countries (all $n = 17$), followed by France ($n = 7$), Belgium and the United Kingdom (both $n = 6$). The most productive collaborative network in the field of CM research was established between China/Australia ($n = 15$), followed by France/Belgium ($n = 4$) and Italy/Belgium ($n = 4$). Japan had with 2/286 (0.7%) the smallest percentage of joint CM items in relation to its total output. Investigators in 46 (60.5%) countries were not involved in any international CM collaborations. Of those, Taiwanese authors had the largest number of publications on CMs ($n = 51$), followed by academics from Russia ($n = 22$) and Greece ($n = 16$).

Most productive research institutions and individual authors

All 2463 CM papers were critically evaluated in relation to their institutions of origin and contributing authors. The ten most productive institutions in the world were located in Japan, the USA, China, France and the United Kingdom (Fig. 4a). The ten most productive authors (appearing anywhere in the author list) in the field of CM-related research either came from Japan or China (Fig. 4b).

Scientific subject categories and document types

Subject categories are defined standard categories in the Web of Science™ database, which represent general areas of science. These categories were distributed by the Journal Citation Reports™ for each scientific journal and its publications. Most articles relating to CM research were assigned to the subject categories "GASTROENTEROLOGY/HEPATOLOGY" ($n = 2133$), "SURGERY" ($n = 1425$) and "PEDIATRICS" ($n = 1136$). Document types of the 2463 identified papers in the field of CM research were classified as original articles (71.0%), meeting abstracts and proceedings (12.9%), reviews (7.7%), editorials and letters (4.3%), case reports (3.7%) and others (0.4%).

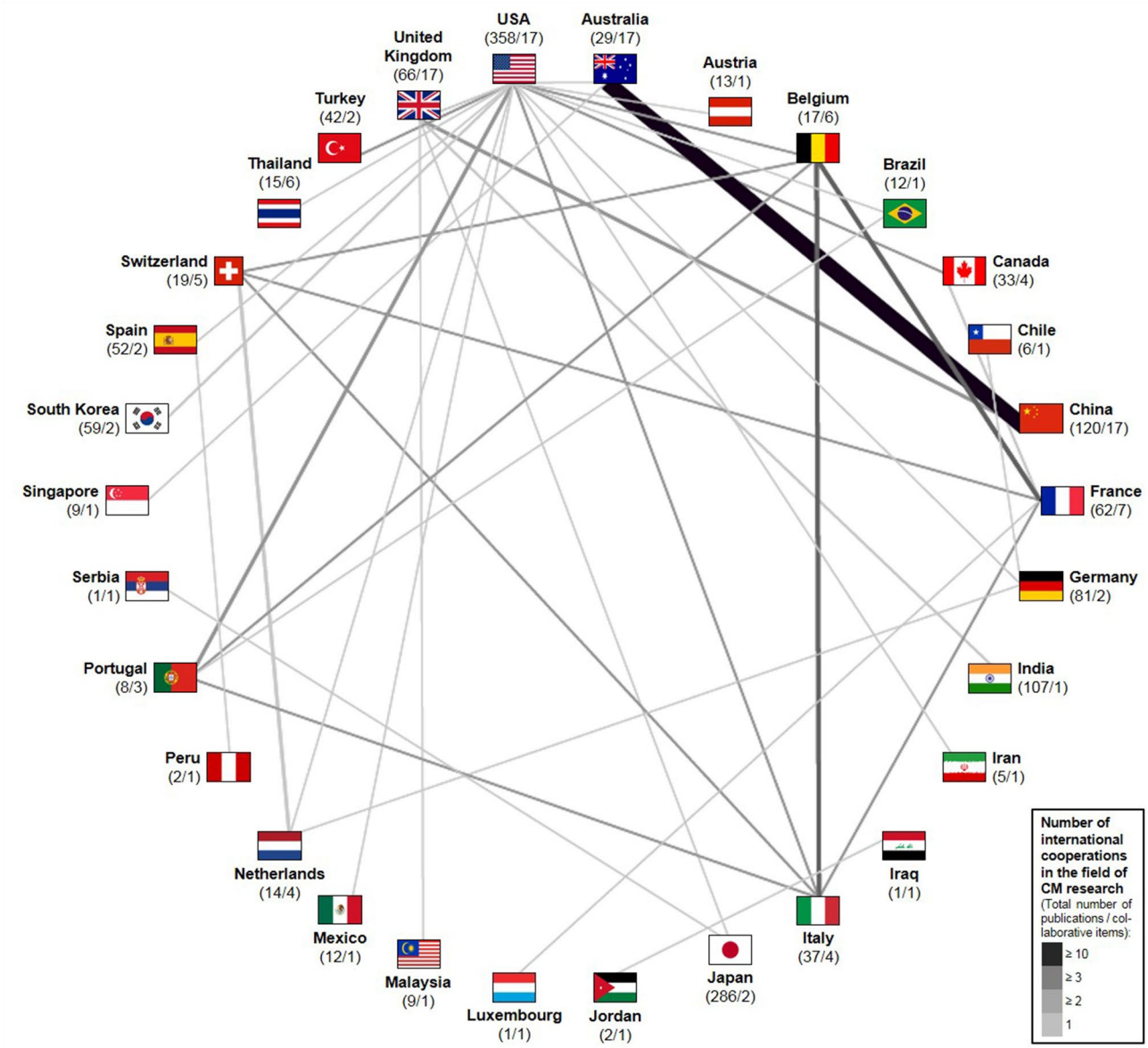

Fig. 3 Network diagram of international collaborations and cooperation publications relating to CMs

Notable scientific journals and publications

All scientific journals listed in the Web of Science™ database were examined in regard to their individual output relating to CM research and citation rates of their published articles were determined. The 2463 papers on CM were published in 820 different journals with an average citation rate of 10.0 (range 0–799) per published item (*h*-index 65). The "*Journal of Pediatric Surgery*" was identified as the most productive journal ($n = 133$), whereas the "*American Journal of Surgery*" had with 70.6 the highest average citation rate per published CM article (Fig. 5). Table 1 lists the ten most-cited publications in the field of CM research.

Discussion

There has been a nearly 19-fold increase in CM-related publications since the 1960s, replicating other pediatric surgical conditions such as congenital diaphragmatic hernia and Hirschsprung's disease [14, 15]. Probably needless to say [16], the ten most-cited articles on CMs are all fairly old. Seven were published between the 1960s and 1980s, e.g. Todani's [4] and Alonso-Lej's [5] original classifications, Babbitt's [6, 9] and Landing's [8] concepts of etiology, Yamaguchi's [7] literature review and first reports of cancer arising from CMs [11, 12]. All these topics were relevant for the scientific community at the time. Nonetheless, more

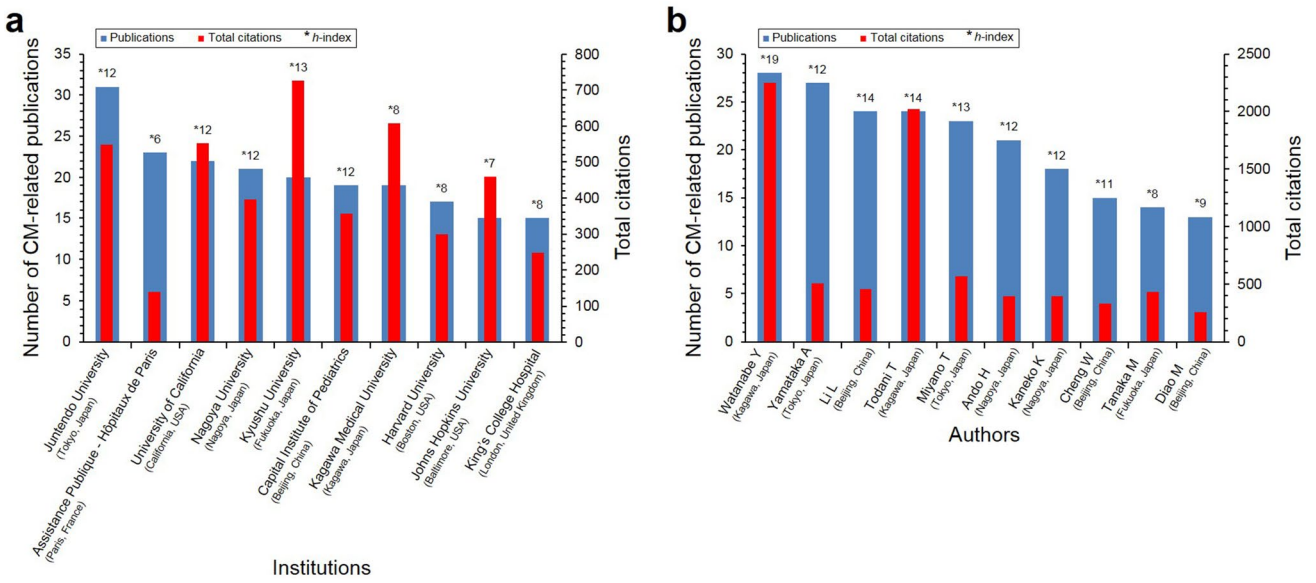

Fig. 4 Ten most productive institutions (**a**) and authors (**b**) in the field of CM-related research

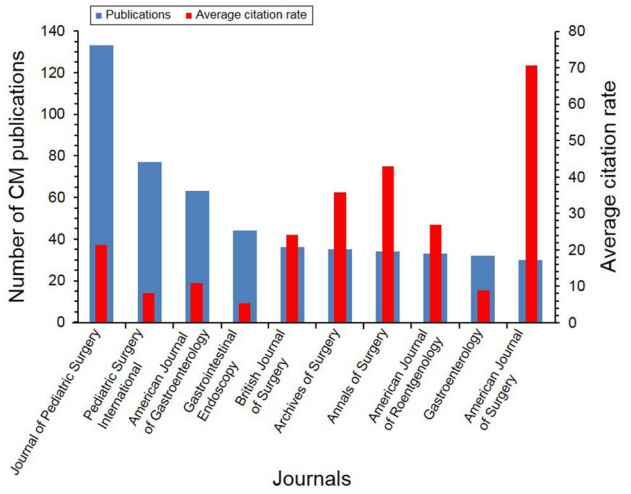

Fig. 5 Ten most productive journals with regard to CM publications and average citation rate per published article

Table 1 Ten most-cited publications in the field of CM research

Rank	Publication	Total citations	Citations per year
1	Todani et al. [4]	799	19.36
2	Alonso-Lej et al. [5]	594	9.95
3	Babbitt [6]	377	7.66
4	Yamaguchi [7]	344	8.97
5	Landing [8]	284	6.33
6	Babbitt et al. [9]	260	5.65
7	Lipsett et al. [10]	212	8.56
8	Todani et al. [11]	203	5.13
9	Voyles et al. [12]	178	5.00
10	Moschcowitz [13]	163	1.44

recent developments in basic science and biomedical technology have not really resulted in a noteworthy advance of CM research and might represent relative scientific stagnation.

Although the USA has produced the largest number of publications in the field of CM research, it is striking that Asian centers have been equally productive, presumably reflecting the known geographical variation in incidence with one paper suggesting (on no actual evidence) that this occurs in about 1 in 1000 births [17]. Certainly, the ten most productive authors in the field either came from Japan or China. Interestingly, Japan had with 0.7% the smallest percentage of collaborative CM items in relation to its total output, but had with 41 one of the highest country-specific *h*-index. This is probably because Japanese clinicians and basic scientists tend to cooperate mainly with their own national colleagues, influenced perhaps because of their efficient and well-funded academic structures. Their *h*-index implies that Japanese researchers have published 41 articles on CMs, each of which has been cited in other papers at least 41 times. With regard to the large number of publications relating to CMs from the USA—globally, they are known to dominate medical and scientific publishing [18, 19]. Additionally, American authors and reviewers tend to bias their citation practice toward articles from the USA [20, 21]. Overall, this finding mirrors a worldwide trend for a greater volume of scientific papers to originate from high-income countries, and further, for authors from these countries to dominate key roles in authorship.

One possible bias of the present study might be associated with analysis of the *h*-index. This metric has received enormous attention for measuring the quality of scientific work. In this context, it must be considered that self-citation by authors can considerably manipulate its validity. Nevertheless, the *h*-index is an established tool to compare different authors, institutions or countries working in one specific scientific field [22]. We also chose to include *h*-index analysis, because it was not relevant to classify CM publications according to the "*Level of Evidence*" as per the Oxford index [23] due to the nature of pediatric surgical research in general. Evidence in this area rarely reaches a high level, even for the common conditions, leading to some authors suggesting a better classification for pediatric surgery reflecting its mainly clinical bias [24].

Areas for debate

Terminology

The term "*choledochal cyst*" should be confined to those with clear extrahepatic cystic (i.e., spherical or globular) change. Trying to use this to describe obviously non-cystic variants—alternatively described as fusiform, cylindrical or spindle-shaped CMs—is clumsy and ignorant of the actual meaning and derivation from its Greek parent (Κύστη—meaning "bladder" or "bladder-shaped") [25, 26]. We (and other authors [27]) therefore prefer more generic terms such as CM or congenital choledochal dilatation and have used the latter throughout.

Incidence

The true incidence of CMs remains unknown and anything in the literature is nothing but guesswork. Nonetheless, we do know that in those patients that present early, it is much less common than biliary atresia (with an approximate but consistent incidence of 1 in 15,000–20,000 births in Europe and North America). We also know that there is a marked geographical and gender variation with a substantially higher incidence in Asian populations and a female predominance of around 4:1 [28–31]. None of this has yet been explained.

Classification

Various morphological classifications of CMs have been proposed over the years. The original classification was described by Alonso-Lej et al. [5] following a literature review of almost 100 cases (type 1, 2 and 3 CM) up until the 1950s. The most widely quoted classification remains the one by Japanese authors Todani et al. [4], based on eight distinct variants (type Ia, b and c; II; III; IVa and IVb and V CM). Our own, the King's College Hospital classification (used since 1995) is a distillation of Todani's classification, concentrating on the three commonest variants: cystic and fusiform extrahepatic dilatation (type 1C and 1F CM) and either of the foregoing in combination with intrahepatic duct dilatation (type 4 CM) [26, 28, 29, 32]. Our original contention is that there is a key difference in presentation and the pathophysiology of the cystic and fusiform variants. This opinion appears also to be gaining traction in the large Chinese centers such as Beijing [33]. Todani's observation that there is something important about where the cystic duct joins the main dilatation (i.e., the difference between type Ia and Ib CMs) has little real relevance—neither clinically nor pathophysiologically. Whereas it has been shown that there are clear clinical and physiological differences between cystic and fusiform variants [34, 35].

Type 4 CMs are found in approximately 10–20% of large cohort studies and it is arguable whether this is simply the natural history of untreated type 1C and 1F CMs or intrahepatic dilatation from the start. Without doubt, intrahepatic dilatation considerably diminishes, at least in children, following effective decompressive surgery. Our series of over 40 children with type 4 CMs that were regularly followed-up by ultrasonography has certainly shown a considerable reduction in intrahepatic duct dilatation, typically within the first year after surgery [36].

Whether the "*choledochocele*" (type 3 CM) should be included at all in any classification has been the subject of a recent North American study [37]. The authors argued that there were so many substantial differences when compared with type 1, 2 and 4 CMs, particularly age at presentation (invariably as an adult) and gender (predominantly male) that it barely merited the term "*congenital*". Certainly, the distinction between this and a long-standing dilatation of the common channel, coupled with a degree of ampullary stenosis, is difficult.

It is worthwhile pointing out that "*Caroli's disease*" (alternatively syndrome if involving the entire intrahepatic tree and coexisting with congenital hepatic fibrosis) remains apart from most choledochal classifications—although it is true that one of its main components is multiple, usually small saccular intrahepatic biliary dilatations. But, unlike any other dilatation, it is a hepatic manifestation of a genetic disease affecting the basement membrane of other organs [mainly the kidney, presenting as autosomal polycystic kidney disease (dominant and recessive), medullary sponge kidney and medullary cystic disease] [38]. The major clinical features of Caroli's disease are recurrent cholangitis, liver cirrhosis and cholangiocarcinoma [39, 40]. Diagnosis depends on showing that the cystic liver lesions are in continuity with the biliary tree, thus differentiating Caroli's disease from primary sclerosing cholangitis and polycystic liver disease [39]. In diffuse Caroli's disease, treatment involves internal biliary bypass procedures and liver transplantation.

There are true type 5 congenital CMs, distinct from Caroli's disease, and these are usually solitary and capable of being detected prenatally.

Literally outside of this, but very much part of the pathology in many variants is the so called "*common pancreatobiliary channel*". This is caused by late gestational failure of the absorption of the ventral pancreatic duct, carrying with it the nascent bile duct into the wall of the duodenum. It therefore negates one of the key functions of the ampulla of Vater and its sphincters of keeping the potentially proteolytic broth of pancreatic juice and bile separate until the duodenal lumen. If the connection is wide enough then bile may enter the domain of the pancreas, and initiate the cascade of pancreatitis or alternatively pancreatic juice refluxes within the confines of the choledochus. Komi et al. [41] have classified variants of the common channel based on angle of insertion etc., but these do not seem to have much functional relevance.

A further pancreatobiliary variant is the "*forme fruste CM*". This term was first coined by Lilly et al. [42] in 1985 and used to describe an entity without (cystic) extrahepatic bile duct dilatation but with a long common channel. However, all four cases were also very abnormal with intrahepatic cysts, stone formation and mild common bile duct dilatation so whether this distinctive phrase is ever needed is arguable. Certainly, pediatric patients with truly isolated long common channels do exist, but often there is a modest fusiform dilatation of their common bile duct and typically they present with pancreatitis [43–45]. This variant is currently not considered under any CM classification and yet it probably falls under the same umbrella. Complete relief after disconnection surgery is reported [45, 46].

Etiology

Although the etiology of many CMs remains disputed, certain elements in their natural history have become clearer. There are two competing hypotheses which seek to explain type 1 and 4 CMs: "*the obstructing segment hypothesis*" and "*the pancreatic reflux hypothesis*". The former one maintains that there is a true congenital narrow distal segment, which leads to proximal, pressure-led dilatation [35, 47]. This would be analogous to the dilated proximal pouch of an esophageal atresia and supported both by direct surgical observation of often tiny distal ducts beyond the gross cystic dilatation coming to early surgery and the replication of the same in fetal animal models by distal duct ligation [48]. The latter hypothesis is certainly imaginative and was postulated by the American radiologist Donald Babbitt. It was based on his observation that during operative cholangiography contrast refluxes into the pancreatic duct via the common channel. He reasoned that the reverse could happen during life and expose biliary epithelium to the destructive effects of activated proteolytic pancreatic enzymes, thus causing weakness and then dilatation of the common bile duct over time [6, 9]. Interestingly, animal models re-directing pancreas juice via the bile duct produce a degree of dilatation but not much [48]. Our own intraoperative observations linking bile amylase levels (as a surrogate marker of reflux), intracholedochal pressure and biliary epithelial histology demonstrated conclusively that it is pressure, which is related to histological mucosal injury and that there is a marked inverse relationship between pressure and reflux [34, 35]. There is also a distinction, which can be drawn between the type 1C and 1F CMs. The latter being high-level refluxers at low pressures. Furthermore, those identified as type 4 CM (whether of cystic or fusiform parentage) tended to be older, had the highest pressures and post-operatively diminished in size once the intraluminal pressure was relieved by a Roux loop [36]. So far, there has been little further basic science or research into the etiology of CMs.

Predisposition to malignant change and cancer risk

The long-term risk of malignant transformation in CMs has been well described and forms the basis for the accepted treatment being surgical excision and reconstruction with a Roux loop [10, 49–53]. A carcinoma may develop anywhere along the biliary tract, but typically it would involve the preoperatively dilated segments; or post-resection, the anastomosis and any residual biliary epithelium in the liver or head of pancreas. Malignant change is probably due to chronic epithelial inflammation, exacerbated by recurrent cholangitis and stone formation [27], and normally takes many years to develop. A mixture of refluxing pancreatic and bile secretions are also thought to promote malignant transformation [54] and even without bile duct dilatation can be associated with an increased incidence of gallbladder carcinoma [55, 56]. The youngest patient to date with an associated malignancy was a 3-year-old Japanese boy, who presented with an invasive cholangiocarcinoma in a type 1 CM [57]. Tanaka et al. [58] identified a total of 11 patients younger than 20 years, who were found to have an adenocarcinoma in the CM at the time of the initial operation. The most common type was a type 4 CM. The main limitation of the literature is a short postoperative follow-up period of cases with CMs, from which it is difficult to extrapolate life-time risk of malignancy. The assumption is that the risk of malignant transformation in CMs is high and therefore all treated children and adolescents should be followed-up long-term with annual controls of CA19-9, abdominal ultrasonography [59], and more invasive investigations if there is evidence of intrahepatic biliary dilatation or presence of stones and debris. There have been a total of 31 cases of cholangiocarcinoma reported in the literature that occurred after a median of 6 years (range 1–34 years)

following resection of a CM [60]. A recent study on resected intrahepatic ducts and epithelial markers in children with CMs has failed to identify a group at greater risk of malignant change and hence such surveillance should probably be non-selective [61].

Minimally invasive treatment

In common with many areas in pediatric surgery, various groups have reported their experience of minimally invasive hepatobiliary surgery in infants and children. In 1995, Farello et al. [62] first described the laparoscopic resection of a CM in a 6-year-old girl. Since then, laparoscopic excision and biliary reconstruction has been adopted by many groups across the globe, but particularly in Asia. Originally, the principles of open surgery were followed: (1) laparoscopic excision of the dilated part of the extrahepatic biliary tree, (2) clearance of the intrahepatic ducts of debris and stones (best achieved with on-table cholangioscopy), (3) clearance of the common channel of debris (though a transduodenal sphincteroplasty is harder to achieve), (4) creation of a long (40–50 cm) Roux-en-Y loop after exteriorization of the small bowel via the umbilical incision and (5) hepaticojejunostomy—the most technically difficult part. Recently, the primacy of the Roux loop has been challenged by some surgeons, being replaced by the technically easier hepaticoduodenostomy [63–65]. This has to be decried as false economy given the much higher incidence of gastric bile reflux and even potential predisposition to malignancy observed in the past by proponents of hepaticojejunostomy such as Todani as part of an *open* procedure [66–68].

Pediatric surgeons from China [69, 70], Japan [71, 72] and Vietnam [73] have perhaps the most experience in minimally invasive surgery for CMs and fully advocate the approach as safe and with equivalent outcomes but with the advantage of a superior cosmetic appearance [74]. The key difference of course is case-mix and volume with much higher numbers going through Asian centers. In general, complication rates in North American and European CM publications appear higher compared to studies from Asia. Robot-assisted resection of CMs has been reported by specialized departments in the USA and the United Kingdom [75, 76]. Although not a realistic proposition for most surgical units, those who have used the robot claim it is superior in dissection and intracorporeal suturing [77]. Open surgery therefore remains the standard to compare to with a proven long-term safety record [78].

Conclusions

CM-related research has progressed from simple observation and documentation of choledochal variations through to a huge accumulation of clinical experience and consequent surgical management. However, studies into underlying etiology and pathogenesis of CMs remain distinctly uncommon, ironically from those (often Chinese) institutions that are now reporting large clinical series.

Acknowledgements The authors thank the medical staff librarians at the Weston Education Centre Library of King's College London for their outstanding support in the literature search process for this manuscript.

Funding No external funding was received by any of the authors in support of this work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This review article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study informed consent was not required.

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