

Review

Clinical Characteristics, Evaluation, Treatment, and Prognosis of Cryptogenic Cirrhosis

Khalid Al Ghamdi ^{1*}, Rozana Bawareth ¹, Abdulkarim Alqufayi ², Raqhdah Alshamase ³, Mohammad Algarni ⁴, Abdulaziz Alshehri ⁵, Nawaf Alshahrani ⁶, Jamayel Alatawi ⁷, Waleed Allahiani ⁸, Faisal Alhadlaq ⁹, Ghaith Alabdullatif ⁹, Rawan Alharbi ¹⁰

¹ Department of Gastroenterology, King Fahad General Hospital, Jeddah, Saudi Arabia

² Department of Internal Medicine, King Khalid Hospital, Hail, Saudi Arabia

³ General Dentist, AlKhaffi General Hospital, AlKhaffi, Saudi Arabia

⁴ Primary Healthcare Center, Ministry of Health, Rabigh, Saudi Arabia

⁵ Department of Emergency Medicine, Ahad Rafidha General Hospital, Abha, Saudi Arabia

⁶ College of Medicine, King Khalid University, Abha, Saudi Arabia

⁷ Department of Internal Medicine, Salmaniya Medical Complex, Manama, Bahrain

⁸ College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

⁹ College of Medicine, Shaqra University, Shaqra, Saudi Arabia

¹⁰ College of Medicine, Taibah University, Medina, Saudi Arabia

Correspondence should be addressed to **Khalid Al Ghamdi**, Department of Gastroenterology, King Fahad General Hospital, Jeddah, Saudi Arabia. Email: k.m.a02@hotmail.com

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Received: 12 September 2022, Accepted: 18 September 2022, Revised: 22 September 2022, Published: 28 September 2022

Abstract

The term cryptogenic cirrhosis (CC) implies that the underlying etiology is uncertain and devoid of definitive clinical, serological, and histological criteria for a specific type of cirrhosis. CC denotes a spectrum of underlying causes, among whom, the majority of evidence implicates non-alcoholic steatohepatitis (NASH) led progression as the most frequent route. CC is held accountable for around 5% of cirrhosis cases today. Cirrhosis complications like liver failure and hepatocellular carcinoma appear as the first presenting feature of the disease, as in other hepatic diseases. The hepatocarcinogenic risk of CC is substantial, with hepatocellular carcinoma's reported annual cumulative incidence ranging between 2.6% to 3.5%. The diagnosis of CC relies on the exclusion of distinctly recognizable diseases and involves a careful clinical assessment including risk history and family history, followed by laboratory testing including serology, autoantibodies, immunoglobulin concentrations, biomarkers for Wilson's disease and Celiac disease, and lastly histological assessment for the prominent type and inflammation distribution, and typical presenting features of cirrhotic tissues. The definitive treatment of CC involves transplantation. In cases suspected to be linked with NASH, medical management until transplantation can be beneficial to the patient. The management of CC involves collaboration of primary care with gastroenterology, hepatology, and transplant consultation, and nutritional counseling. Data regarding survival post-transplantation is limited and has shown conflicting results.

Keywords: cryptogenic cirrhosis, non-alcoholic steatohepatitis, orthotopic liver transplantation

Introduction

Liver cirrhosis is the common end-stage of etiologically varied chronic hepatic disorders, with distinct geographical distribution, that may pursue an indolent path and stay asymptomatic until complications arise or get discovered incidentally at necropsy (1). The term cryptogenic cirrhosis (CC) implies that the underlying etiology is uncertain and devoid of definitive clinical, serological, and histological criteria for a specific type of cirrhosis. CC is therefore a diagnosis of exclusion. CC denotes a spectrum of underlying causes, among whom, the majority of evidence implicates non-alcoholic steatohepatitis (NASH) led progression as the most frequent route (2). Nevertheless, current findings from histological and epidemiological research also list other etiological factors like slow progressing, chronic autoimmune hepatitis including occult inflammatory biliary disease, non-B non-C viral hepatitis, occult ethanol intake, and hepatic vascular disease (2, 3). CC was held accountable for around 5% to 30% of cirrhosis cases in earlier, but today, with diagnostic advances in viral hepatitis testing for serological and other biomarkers, the actual prevalence is estimated to be much lower at 5% (4). Women are noted to be slightly more predisposed to the condition, with the average age at diagnosis being 60 years (5). In the United States of America, the percentage of CC patients was reported to be roughly 4%, according to the United Network of Organ Sharing (UNOS) database for patients awaiting liver transplantation (6), although other registries in the United States of America indicate a significant prevalence of “unknown/other” etiologies of liver transplantation in adult and pediatric patients (7).

Methodology

No specific criteria were selected beforehand to determine which publications would be incorporated in this review as the objective was to be as comprehensive as possible. PubMed and Google Scholar search engines were utilized to look for scientific publications containing “cryptogenic cirrhosis”, “cryptogenic liver disease”, and “cryptogenic liver cirrhosis”. After a preliminary scanning of abstracts, full-lengths of relevant articles from peer-reviewed journals were acquired. The references sections of these articles were also screened for pertinent citations which were referred to for additional review.

Discussion

Clinical characteristics

Comparative studies of CC with viral hepatitis related cirrhosis have shown a higher prevalence of female gender, of metabolic derangements, of cardiovascular conditions, extrahepatic neoplasms, and lower serum aminotransferases levels (8). These studies have found a concurrence of full-scale metabolic syndrome or isolated characteristics mainly overweight/obesity, that are not traditionally seen in other types of cirrhosis, and a greater rate of cardiovascular conditions (9, 10). This observation corresponds with the current medical consensus of a fundamentally metabolic etiology underlying CC pathogenesis in the majority of cases. Other accompanying features seen in such patients include hyperuricemia, which is a risk factor for non-alcoholic fatty liver disease (NAFLD) (11) and higher intermittent fasting glucose/type 2 diabetes, although type 2 diabetes often develops as a sequela of cirrhosis rather than preceding it (12). Coexisting hypothyroidism and cholelithiasis/cholecystectomy has also been observed to be more prevalent in CC rather than other cirrhosis forms (13, 14). The natural history of CC, with respect to morbidity and mortality, has been sparsely studied so far, with variable results (8). Cirrhosis complications like liver failure and hepatocellular carcinoma appear as the first presenting feature of the disease, as in other hepatic diseases (8). The hepatocarcinogenic risk of CC is substantial, with hepatocellular carcinoma’s reported annual cumulative incidence ranging between 2.6% to 3.5% (8, 15, 16). According to one case series, 45% cases present with only abstract symptoms such as fatigue, or formerly unexplained laboratory aberrations like reduced platelet count (17). In 45% cases, portal hypertension related complications like recent onset ascites, variceal hemorrhage, and encephalopathy were noted as presenting features (17). In rare cases, new-onset subacute hepatic failure can be seen in obese patients with formerly unrecognized cirrhosis (18). As mentioned earlier, aminotransferases levels are usually only modestly elevated or normal in CC cases. One study, particularly, showed that in cases succeeding NASH, a substantial decrease in steatosis runs parallel to falling aminotransferases levels and rising fibrosis (19). Consequently, CC arising from NASH demonstrates one end of the process. That being said, generally, aminotransferases and alkaline phosphatase irregularity patterns have been utilized to categorize CC as more or

less probable to have originated fundamentally from NASH, autoimmune hepatitis, or biliary disease (20, 21).

Evaluation

The diagnosis of CC relies on the exclusion of distinctly recognizable diseases. The diagnosis starts with a meticulous clinical assessment. The risk history for viral hepatitis like previous intravenous drug usage and familial history for hepatic disorders is crucial. In this regard, a familial association between NASH and CC has been discovered (22). Examination of the present and past cumulative ethanol intake, present or past obesity, and related metabolic conditions such as diabetes mellitus, hyperlipidemia and a medical history of prior unaccountable hepatic enzyme aberrations or known history of fatty liver is also deemed necessary. The latter requires direct questioning since the fatty liver diagnosis may have been arrived at many years earlier than that of cirrhosis and may not be still remembered by the patient. History of medication usage such as methotrexate is also essential. Interestingly, NASH-methotrexate synergism has been implicated in methotrexate associated hepatic damage (23). Since metabolic disturbances arising from cirrhosis may induce body mass loss, it is important to find the mean adult weight before disease onset (24).

Laboratory investigations for CC involve viral serologies, autoantibody assays, quantitative immunoglobulin concentrations, iron indices, alpha-1-antitrypsin (A1A) phenotype and concentration, Wilson disease biomarkers, and potentially celiac disease biomarkers (25).

Aminotransferase concentrations, like aspartate transaminase and alanine transaminase, as discussed priorly, are generally only modestly increased or normal in CC cases. A definitive diagnosis can be made based on a biopsy. However, there are certain limitations to these investigations. Antinuclear antibodies maybe be identified in one third of NASH cases, therefore they are not considered to be highly specific for autoimmune conditions (26). Heterozygosity of abnormal A1A in patients with normal levels or histological demonstration of A1A deficiency can be observed in nearly 20% of CC patients, however, it is not substantially different from a control group (17, 27). Wilson disease biomarkers are often not investigated in older cases but literature reports of exceptions where older patients tested positive for Wilson's disease biomarkers. Specificity of quantitative immunoglobulins is not very high, but they can guide diagnosis as atypical elevation of IgG is indicative of an autoimmune activity and atypically increased IgA

indicates steatohepatitis (17, 28). IgA accumulation in the liver has been observed in both alcohol-associated and diabetes-linked steatohepatitis (29).

Histological evaluation is not always achievable in severe cases but may aid in identifying the cause based on remanent traces of pre-existing conditions (20, 21). But understanding the findings of the histological examination under these circumstances demands tight collaboration between the physician and the pathologist to ensure correct evaluation. Researchers have reported identifying remanent histological observations in cases with previous biopsy displaying incontrovertible NASH that have undergone re-evaluation for advanced stage cirrhosis with inadequate indicators for a steatohepatitis diagnosis (30-32). In such cases, macrosteatosis foci, cellular ballooning as well as glycogenated nuclei persist as remnants of previous steatohepatitis in cirrhotic cases where biopsy was deficient of definite indicators for NASH but that showed a compatible medical history and a previous biopsy demonstrating clear NASH.

A classification of CC based on clinical and histopathological features widely used today was adopted from previous literature (20, 21, 33, 34). The first type of CC is based on the presence of characteristics of steatohepatitis like scattered foci of macrosteatosis, occasional hepatocytic ballooning with Mallory-Denk bodies, megamitochondria, and glycogenated nuclei, commonly with a history of obesity and insulin-resistance. Familial history of hepatic disease is frequently present. According to the existence of this advanced stage of NASH, stage 4 NASH is further categorized as NASH with cirrhosis, cirrhosis with NASH characteristics, and bland cirrhosis with predisposition to NASH (metabolic features like obesity, diabetes, and hyperlipidemia). The second type of CC consists of cirrhosis with manifestations of autoimmune disorder such as portal inflammation, plasma cells, or granulomas. Individuals can display significant autoimmune score and familial history of autoimmune illness is prevalent in such cases. The third category is of occult viral hepatitis like post-necrotic hepatitis B or presently unknown viral infection (non-B, non-C hepatitis). Risk history can comprise percutaneous routes involving previous blood transfusion and intravenous drug usage. Histologic features potentially comprise high prevalence of mononuclear inflammation, and lymphoid follicles. Fourth type of CC is cirrhosis with long-standing history of high alcohol intake but with a below threshold intake on an everyday or weekly basis. This needs a meticulous evaluation of previous exposure

including cumulative consumption over life. Faint presence of glycogenated nuclei and insulin receptor staining may differentiate NASH from alcoholic steatohepatitis. The fifth type of CC displays characteristics of biliary disease such as bile ductular proliferation as well as cholestasis. Lastly, the sixth category of CC is bland cirrhosis which is simply a term given to cirrhosis that is devoid of other distinguishing characteristics and detectable risks.

Treatment

The definitive solution of CC involves transplantation. In cases suspected to be linked with NASH, medical management until transplantation can be beneficial to the patient (12, 21). Change in lifestyle and behavioural modifications such as physical exercise, body weight management, and a nutritious diet are suggested. Similarly, in cases suspected of arising from other etiologies, using targeted treatment approaches can help in the pre-transplant intermediate management of the disease(3).

Presently, CC is the fourth most frequent indication for orthotopic liver transplantation (OLT) (4). There are, however, only a limited number of case series in the literature on the long-term outcomes of OLT for CC (35-37). Studies have shown lower acute rejection rates than for transplants performed for other causes (38). Further, substantially lesser incidences of infection and postsurgical kidney dysfunction are seen. Other postsurgical complications including arterial thrombosis and biliary fistulae, however, have similar prevalence rates as with OLTs performed for other reasons (38). Few researchers have studied the frequency and severity of disease recurrences in OLT grafts. The proportion of sample that develops chronic hepatitis of unknown origin ranges between 0% and 43% across literature (39, 40). One study comparing hepatitis occurrence in OLT indicated for CC and other causes found a 22% incidence of chronic active hepatitis or steatohepatitis in the former cohort. Similarly, another study found a chronic graft rejection incidence rate of 25% and disease recurrence rate of 4%, though it is not always possible to differentiate between the two outcomes from a pathological viewpoint. The incidence of chronic hepatitis is much greater for CC as compared to all other etiologies with the exception of hepatitis C related cirrhosis. Nevertheless, the retransplantation incidence rate for chronic graft rejection and/or recurrence was close to that for the control group (4% vs 5.9%).

As mentioned earlier, a CC diagnosis predisposes to hepatocellular carcinoma development (16). Due to this, it is advised that patients be monitored using hepatic ultrasound imaging biannually for hepatocellular carcinoma. Other screening procedures such as computed tomography imaging, and magnetic resonance imaging may also aid in detection. Additionally, alpha-fetoprotein investigation can oftentimes supplement ultrasound imaging (10).

The management of a CC case involves intertwining of primary care with gastroenterology, hepatology, and transplant consultation, and nutritional counseling (3). A primary care doctor has a crucial part in recognizing patients prone to cirrhosis or liver disease and ordering the necessary investigations that will aid in diagnosing before the involvement of specialists. Gastroenterology consult will be able to manage care of CC patients and detect complications related with CC like esophageal varices through endoscopic visualization. Hepatology consult will aid in administering further therapeutic interventions as the liver disease progresses. Transplant hepatology and surgical consult will contribute to planning the OLT procedure, once the candidate is approved for it. This includes laboratory investigations, imaging, and medical history recording. Lastly, nutritional counseling is essential for CC, as majority of the cases have shown a relation to NASH. Metabolic disturbances such as diabetes mellitus, hyperlipidemia and obesity are considered to be linked with CC development (9).

Prognosis

In one study, researchers observed a 39.2% mortality rate in CC as compared to a 30% rate in hepatitis C related cirrhosis over a median follow-up duration of 42 months (8). Further, for CC, the median survival duration was noted to be 60 months (8). The decision for OLT is based on the Model for End-Stage Liver Disease (MELD) score which uses parameters such as creatinine, bilirubin, international normalized ratio and sodium to calculate a score which is used to judge the seriousness of end-stage hepatic disease and necessity for OLT (41).

Data regarding survival post-transplantation is limited and has shown conflicting results. In one series, three-, five-, and ten-years survival rates were lesser than those in the control cohort, which the authors suspected was possibly due to the greater postsurgical mortality rate of 20% (38). On the 15- and 20- years mark, the survivals were comparable with those indicated liver transplants for other conditions. Individual case survival showed

association to donor graft features. It was lesser in patient with below optimal organs, however, the series failed to show significance due to small sample size (38).

Conclusion

A diagnosis of cryptogenic liver disease can be a life changing. CC continues to be a multifactorial and heterogenous disease, a problem for both physicians and researchers. It requires more research to understand its etiopathogenesis and natural history. More data is needed to define risk factors, enhance characterizing of the subtypes, and confirm etiologic relationship. Also, research is needed on post-transplant outcomes and survival in the context of different population groups. Histopathological re-investigation of the explanted cirrhotic tissue can render potential leads in many cases where other diagnoses were previously excluded from consideration. With novel advances in the domain of hepatology, it may be possible to understand this disease further, optimize patient care and improve long-term outcomes in those undergoing OLT.

Disclosure

Statement

The authors declare no conflict of interest.

Funding

No funding.

Ethical consideration

Non-applicable.

Data availability

Data that support the findings of this study are embedded within the manuscript.

Authors' contribution

All authors contributed equally to the drafting, writing, sourcing, article screening and final proofreading of the manuscript.

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