Factors contributing to diagnostic delay of Caroli syndrome: a single-center, retrospective study

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Wen Shi
Peking Union Medical College Hospital

Xiao-ming Huang
Peking Union Medical College Hospital

Yun-lu Feng
Peking Union Medical College Hospital

Feng-dan Wang
Peking Union Medical College Hospital

Xiao-xing Gao
Peking Union Medical College Hospital

Yang Jiao ⊗ peterpumch@163.com
Peking Union Medical College Hospital

Corresponding Author
ORCID: 0000-0003-3957-3829

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Abstract

Background Caroli syndrome (CS) is a rare congenital disorder without pathognomonic clinical symptoms or laboratory findings. Imaging modalities are first-line diagnostic methods.

Methods A retrospective analysis was conducted on CS patients admitted to a single tertiary medical center in Mainland China. The diagnostic timelines of CS patients were reviewed to demonstrate the initial findings at diagnosis of CS, the risk factors associated with diagnostic delay, and potential clues leading to early diagnosis.

Results The median diagnostic delay was 1.75 years (range: 1 month to 29 years, interquartile range: 6.2 years) in sixteen enrolled CS patients. Sex, age, and initial symptoms were not associated with diagnostic delay. 87.5% of CS patients were diagnosed by imaging, and the accuracy of ultrasonography, computed tomography (CT), and magnetic resonance cholangiopancreatography was 25%, 69.2%, and 83.3%, respectively. The median diagnostic delays for patients with or without CT performed at the first hospital visited according to physician and radiologist suspicion of the diagnosis were 7.4 months and 6 years, respectively (p=0.021). Hepatic cysts with splenomegaly were found by ultrasound in over half of CS patients.

Conclusions The majority of CS patients were not diagnosed until complications of portal hypertension had already developed due to the non-specific clinical presentations, rarity, and therefore low index of suspicion for CS. Some patients had positive autoantibodies, which can lead to misdiagnosis. Recognition and early suspicion of the disease were important factors influencing diagnostic delay of CS. Hepatic cysts plus splenomegaly detected by US, which is almost always the first imaging test, might provide a clinical clue to include CS in the differential diagnosis.
Introduction

Caroli syndrome (CS) is a rare congenital disorder characterized by segmental dilatation of the intrahepatic ducts and hepatic fibrosis [1]. The incidence of CS is estimated to be 1 per million of the population [2]. Although the pathoetiologicial details are still poorly understood, CS is now known to be an autosomal recessive hereditary disorder involving malformation of the ductal plates and periportal fibrosis [3].

CS has no pathognomonic clinical symptoms or signs [4]. It can manifest insidiously, with patients presenting in two main ways: intrahepatic ductal ectasia and bile stagnation (i.e., recurrent cholangitis and/or cholangiolithiasis) or portal hypertension (i.e., hypersplenism, gastrointestinal bleeding, ascites) [5]. CS has also been reported in association with cystic renal disease, pancreatic cysts, cavernomatous transformation of the portal vein, and an increased risk of cholangiocarcinoma [6].

Histopathology is useful for securing a definitive diagnosis, but imaging modalities including ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) remain the first-line diagnostic methods due to their noninvasiveness and convenience [7]. Although early diagnosis of CS is the first step to early interventional, complication control, and surveillance, there is scarce evidence on the clinical parameters that influence early diagnosis or how imaging and their features might influence the diagnostic timeline of CS patients [8].

We therefore performed a single-center retrospective study to review the diagnostic timelines of 16 CS patients to investigate the clinical features at diagnosis of CS, the risk factors associated with diagnostic delay, and potential clues leading to early diagnosis.

Methods

Sixteen CS patients were admitted to Peking Union Medical College Hospital between
January 1 2005 and August 1 2019. Demographic data, symptoms, laboratory results, detailed imaging findings, associated conditions, histopathology results, and other information related to CS diagnosis including residential location, family history, and hospitals visited were collected from the medical records. A diagnostic timeline was drawn for each patient from these data. We defined diagnostic delay as the time between initial clinical presentation and final diagnosis.

Data were analyzed using SPSS for Windows Version 23.0 (IBM Inc., Chicago, IL). Continuous variables were reported as the mean ± standard deviation (SD) and compared with the t-test if normally distributed according to the Shapiro-Wilk test. Otherwise, they were reported as median values with interquartile ranges (IQR) and compared using the Mann-Whitney U test. Categorical variables were analyzed using the chi-squared test. Both continuous and categorical variables were analyzed using logistic regression or Spearman’s coefficient. A p-value <0.05 was considered statistically significant. Since diagnostic delay was not normally distributed, we took the natural logarithm (ln) of the diagnostic delay (ln (diagnostic delay)), which was normally distributed, allowing the use of t-tests with this variable.

Results

Demographic features

There were 10 male and 6 female CS patients, with a male to female ratio of 5:3. The median age of onset of symptoms was 7 years of age (range: 1 month to 38 years old, IQR: 15.5 years old), the median age of first clinic visit was 10 years old (range: 1 month to 38 year old, IQR: 17.6 years old), and the median age at diagnosis was 15 years old (range: 8 months to 39 years old, IQR: 24.5 years old). The median diagnostic delay, which was defined as the time between initial clinical presentation and final diagnosis, was 1.75 years (range: 1 month to 29 years, IQR: 6.2 years). Sex, age of onset of symptoms, age at
first clinic visit, and age at diagnosis were not significantly associated with diagnostic delay (Table 1).

*Initial clinical presentation*

Initial symptoms of the 16 CS patients included fever (n=6), abdominal pain (n=3), abdominal distention (n=8), gastrointestinal bleeding (n=1), and fatigue (n=1). Most initial symptoms led directly to a first clinic visit, with the exception of three patients who had abdominal distention as the initial symptom but only presented later to hospital for other reasons (Table 2). None of these initial symptoms were associated with diagnostic delay (Table 1). Three patients had a positive family history, but similarly this was not associated with diagnostic delay (Table 1).

*Laboratory findings*

Laboratory findings of the 16 CS patients at diagnosis included decreased peripheral white blood cell count (n=11), anemia (n=11), and decreased platelet count (n=10). Among them, ten patients had pancytopenia. Some patients had abnormal liver function, with elevated serum alanine aminotransferase (ALT) (n=2), elevated serum bilirubin (n=2), decreased serum albumin (n=2), and prolonged prothrombin time (PT) (n=5). Of note, the two patients with elevated ALT had cholangitis when admitted, and their ALT levels returned to normal after anti-microbial treatment. Two patients had increased serum creatinine levels, both of whom had multiple renal cysts.

Positive autoantibodies were present in four CS patients: antinuclear antibodies (ANA) were tested in ten patients and two were positive; anti-mitochondrial antibodies (M2 subtype; AMA-M2) were tested in seven patients and two were positive; and anti-smooth muscle antibodies (SMA) were tested in seven patients and one was positive. Two patients
were initially misdiagnosed as autoimmune disease. The first misdiagnosed patient was a 21-year-old man with positive ANA and slightly elevated aspartate transaminase (AST) and immunoglobulin G (IgG), who was misdiagnosed with autoimmune hepatitis (AIH) and was treated with corticosteroids and azathioprine for one month. There was no clinical improvement, and histopathological examination of his liver biopsy secured a diagnosis of CS. The other misdiagnosed patient was a 33-year-old woman who presented with low-grade fever and abdominal distention who had a positive ANA and AMA-M2 and slightly elevated gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP). She was initially misdiagnosed with primary biliary cirrhosis and treated with corticosteroids plus ursodeoxycholic acid for three months. Again, there was no clinical improvement and she developed recurrent cholangitis. MRCP was performed, and the diagnosis of CS was made according to typical imaging results. Her symptoms were soon controlled with antibiotics and her GGT and ALP returned to normal.

Lower white blood cell (WBC) counts (5 years vs. 4 months; p=0.01), lower platelet (PLT) counts (4.5 years vs. 6.5 months; p=0.01), and pancytopenia (4.5 years vs. 6.5 months; p=0.01) at diagnosis were associated with longer diagnostic delay. There were no other significant associations between laboratory findings and diagnostic delay (Table 1).

**Imaging manifestations**

All 16 CS patients were examined by US before diagnosis, 13 were examined by CT with or without contrast, and 12 by magnetic resonance cholangiopancreatography (MRCP). Some patients had several imaging studies at different hospitals before the final diagnosis was made. On average, US was performed 1.9 times and CT 1.3 times per patient before diagnosis. The accuracy of US, CT, and MRCP modalities was 25%, 69.2%, and 83.3%, respectively (Table 3). Fourteen patients were diagnosed by imaging, while two patients
were finally diagnosed from the histopathological appearances on liver biopsy. All 16 patients had US performed during the first visit to a hospital, while eight patients also had CT scans due to suspicions raised by physicians and radiologists. CT performed at the first hospital visited was associated with statistically significant shorter diagnostic delay \( (p=0.021; \text{Table 1}) \). The median diagnostic delay for patients with CT performed or not performed at the first hospital visit was 7.4 months and 6 years, respectively.

We examined the US signs in patients at their first hospital visit. Diffusive hepatic lesions, hepatic cysts, splenomegaly, and renal cysts were reported in 10 (62.5%), 10 (62.5%), 15 (93.8%), and 8 (50%) patients, respectively. The combination of diffuse hepatic lesions plus splenomegaly, hepatic cysts plus splenomegaly, and renal cysts plus splenomegaly were found in 10 (62.5%), 9 (56.3%), and 8 (50%) patients, respectively (Table 4).

**Diagnostic timelines**

The diagnostic timelines of all 16 patients were drawn to visualize important diagnostic time points, disease phase at diagnosis, and imaging modalities used to make the diagnosis (Figure 1). We divided the CS course into three phases: phase 1 (four patients, 25%), no proof of portal hypertension (i.e., hypersplenism); phase 2 (ten patients, 62.5%), discovered complications of portal hypertension without gastrointestinal varicosity bleeding; and phase 3. (2 patients, 12.5%), at least one recorded variceal bleed.

**Discussion**

Caroli syndrome (CS) is a rare congenital disorder associated with ductal plate malformation and hepatic fibrosis \([9]\). CS has previously been reported to usually be diagnosed during childhood or adolescence but may be diagnosed in adulthood \([10, 11]\), consistent with our findings. 50% of our CS patients developed symptoms before six years
of age, and 18.75% of patients had symptom onset in adulthood. However, only 25% patients were correctly diagnosed before six years and 37.5% patients were not diagnosed until adulthood. The majority of patients already had complications of portal hypertension at the time of diagnosis and some even had severe gastrointestinal bleeding due to esophagogastric varices. There was also a wide range of diagnostic delay in our patients, from 1 month to as long as 29 years. However, to our best knowledge, there is no published evidence on the clinical factors influencing diagnostic delay in CS patients, indicating that diagnostic delay of CS patients might be a severe yet overlooked problem. We therefore attempted to analyze possible factors associated with diagnostic delay in CS patients and whether there were any clues that could facilitate earlier diagnosis.

As previously reported, CS patients can present with fever and abdominal pain due to recurrent cholangitis, fatigue and ecchymosis due to hypersplenism, gastrointestinal bleeding due to varices, and non-specific digestive symptoms such as anorexia and abdominal distention [1, 4]. The most common initial symptom of CS patients in our cohort was non-specific abdominal distention followed by fever, abdominal pain, variceal bleeding, and fatigue. Although three out of the eight patients initially presenting with abdominal distention did not seek immediate medical advice, which might have contributed to the diagnostic delay of CS, there was no significant difference in diagnostic delay between patients with different initial symptoms.

Similarly, the laboratory findings of CS patients were not discriminative. Leukopenia, thrombopenia, and pancytopenia were associated with longer diagnostic delay. However, this was likely to be due to those with longer diagnostic delay more likely to have hypersplenism. Other laboratory abnormalities including increased ALT and bilirubin, decreased albumin, and prolonged PT were not associated with diagnostic delay. Interestingly, autoantibodies were found to be positive in four (25%) of our CS patients,
which has not previously been reported. Although the presence of these autoantibodies is well established in AIH and PBC, there is no reported association of these autoantibodies with CS\cite{12}, which might therefore mislead the diagnosis. Indeed, these positive autoantibody results did lead to, or at least contribute to, the initial misdiagnosis of two CS patients. The coexistence of autoantibodies and CS is important to be aware of, since immunosuppressive therapy might lead to clinical exacerbation of CS.

Imaging studies remain the mainstay diagnostic modality in patients with CS due to their non-invasiveness compared to liver biopsy \cite{1, 4}. Most (87.5\%) of our patients were diagnosed according to typical imaging features by US, CT, and MRI. The diagnosis of CS relies on demonstrating cystic dilatation of intrahepatic bile ducts in continuity with the biliary tree as well as signs of hepatic fibrosis. US features of the liver in CS include intrahepatic cystic anechoic areas in which fibrovascular bundles, stones, and linear bridging or septa may be present \cite{1, 13}. Nevertheless, it is often difficult for radiologists to differentiate intrahepatic cysts caused by CS from cysts of other causes such as polycystic liver disease by US, and interobserver variability in making the diagnosis has been reported according to the experience of the radiologists \cite{13}. In our study, the accuracy of diagnosing CS by US was only 25\%, and some patients were not successfully diagnosed by US at first but were later diagnosed by another US performed in another hospital. Taking this interobserver variance into account, the actual accuracy of US for CS might be even lower. In our study, CT scans were much more accurate than US (69.2\%).

The “central dot sign” on CT (Figure 2), which refers to small foci of strong contrast enhancement within cystic lesions, is thought to correspond to portal radicles bridging dilatations and thus be pathognomonic of CS \cite{14}. MRCP can establish the diagnosis of CS by revealing connections between bile duct ectasias and the normal biliary tract (Figure 3) as well as ruling out other conditions like multiple liver abscesses and polycystic liver
disease [13, 14]. The accuracy of MRCP was 83.3% in our study, similar to previous studies [5, 13]. In our study, patients who had a CT scan performed due to physician or radiologist suspicion at the first hospital visited had a significantly shorter diagnostic delay. This was the only risk factor associated with diagnostic delay in our study, suggesting that a high index of suspicion for the disease might be the most important factor influencing diagnostic delay in CS, whose rarity often leads to an unawareness of the condition and thus misdiagnosis.

US was nearly always the first-line imaging modality due to its cost-effectiveness and convenience, despite its suboptimal accuracy. Splenomegaly, diffusive hepatic lesions, and hepatic cysts were the most common US findings in CS. When combined, diffusive hepatic lesions plus splenomegaly and hepatic cysts plus splenomegaly were found in over half of our CS patients. However, diffusive hepatic lesions plus splenomegaly can also be found in a variety of other conditions including portal hypertension caused by thrombosis or dysplasia of the portal venous system, congenital disorders such as Niemann-Pick disease, congenital hepatic fibrosis other than CS, and even malignancies like lymphoma [15]. Hepatic cysts plus splenomegaly has a narrower differential diagnostic spectrum, mainly other hepatic cystic diseases including polycystic kidney disease [16] and hepatic peribiliary cysts (which only rarely lead to splenomegaly) [17], and, even more rarely, malignant cystic diseases of the liver and spleen which can be easily differentiated [18]. Thus, hepatic cysts plus splenomegaly seen by US might provide a useful clue to physicians and thus might shorten the diagnostic delay of CS.

This study has several limitations. First, the study was retrospective, and although we detected possible risk factors associated with diagnostic delay of CS patients, they require further verification. Second, since CS is rare, the sample was relatively small, and the results require validation in larger samples. Third, we took the natural logarithm of
diagnostic delay to make it normally distributed so that it could be compared using the t-test, which has stronger potency than the U test. Finally, we are a tertiary hospital and this is a single-center study, which could introduce bias in that patients sent to our hospital might be more complicated and difficult to diagnose.

Conclusions

CS can be insidious and there are no distinguishing symptoms or laboratory findings. The majority of patients were not diagnosed until complications of portal hypertension had already developed. Some patients might have positive autoantibodies, which could be deceptive and lead to misdiagnosis. US was not ideally accurate, but hepatic cysts with splenomegaly detected by US might raise the diagnostic index of suspicion for CS. Early suspicion of the disease might be the most important factor influencing diagnostic delay of CS.

Abbreviations

CS: Caroli Syndrome; US: ultrasonography; CT: computed tomography; MRI: magnetic resonance imaging; SD: standard deviation; IQR: interquartile ranges; ALT: alanine aminotransferase; PT: prothrombin time; ANA: antinuclear antibodies; AMA-M2: anti-mitochondrial antibodies (M2 subtype); SMA: anti-smooth muscle antibodies; AST: aspartate transaminase; IgG: immunoglobulin G; AIH: autoimmune hepatitis; GGT: gamma-glutamyltransferase; ALP: alkaline phosphatase; WBC: white blood cell; PLT: platelet; MRPC: magnetic resonance cholangiopancreatography; PBC: primary biliary cholangitis; CT+C: computed tomography with contrast; PET/CT: positron emission tomography/computed tomography; Ln: natural logarithm; DD: diagnostic delay; HGB: hemoglobin.
Declarations

Ethics approval and consent to participate

The study protocol has been approved by the Ethics Committee of Peking Union Medical College Hospital (Ref: S-K 921). Written informed consent was obtained from all patients or their legal guardian about personal and medical data collection and analysis.

Consent to publish

All study participant or their legal guardian provided informed written consent for publication of the case reports and any accompanying images.

Availability of data and materials

The original anonymous dataset is available on request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

All authors were involved in the care of the patients. WS and XG wrote the initial draft of the manuscript. FW assessed all Imaging manifestation. YJ, XH and YF critically appraised and revised the overall content of the manuscript. All authors read and approved the final manuscript.

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Authors’ information

All authors are from Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China. WS and YF are from the Department of Gastroenterology. XH, YJ and XG are from the Department of General
Internal Medicine. FW is from the Department of Radiology.

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splenic cystic malignant fibrous histiocytoma: A case report and literature review. *Int J Surg Case Rep* 2013; 4(1):139-141.

### Tables

Table 1. Association between ln(diagnostic delay) and demographics, initial symptoms, laboratory findings, and image modalities used.

|               | N  | Mean | SD  | p-value |
|---------------|----|------|-----|---------|
| Ln(DD)        |    |      |     |         |
| Male          | 10 | 0.76 | 1.74| p=0.56  |
| Female        | 6  | 0.17 | 2.20|         |
| Age of onset of symptoms | p=0.52 |
| Age of first clinical visit | p=0.99 |
| Age of diagnosis | p=0.17 |
| Fever         | 6  | 0.41 | 2.31|         |
| Not fever     | 10 | 0.61 | 1.70| p=0.84  |
| Abdominal pain|    |      |     |         |
| Not abdominal pain | 13 | 0.52 | 2.00| p=0.93  |
| Abdominal distention|    |      |     |         |
| Not abdominal distention | 8  | 0.84 | 1.39|         |
| Normal WBC    | 5  | -1.47| 1.36|         |
| Decreased WBC | 11 | 1.45 | 1.27| p=0.01  |
| Normal HGB    | 5  | -0.47| 1.57|         |
| Decreased HGB | 11 | 0.99 | 1.89| p=0.16  |
| Normal PLT    | 6  | -0.92| 1.80|         |
| Decreased PLT | 10 | 1.41 | 1.34| p=0.01  |
| No pancytopenia| 6  | -0.92| 1.80|         |
| Pancytopenia  | 10 | 1.41 | 1.34| p=0.01  |
| Normal PT     | 11 | 0.51 | 2.16|         |
| Prolonged PT  | 5  | 0.59 | 1.25| p=0.94  |
| CT at first hospital visited |     |      |     |         |
| No CT at first hospital visited | 8  | 1.62 | 1.33| p=0.02  |

* Calculated and tested by Pearson correlation coefficient

** Initial clinical presentations

Ln: natural logarithm, DD: diagnostic delay, HGB: hemoglobin, PLT: platelet, PT: prothrombin time, SD: standard deviation, WBC: white blood cell

Note: Initial clinical presentations of gastrointestinal bleeding or fatigue, elevated alanine aminotransferase or bilirubin, decreased albumin, positive antinuclear antibody, anti-smooth muscle antibodies, or anti-mitochondrial antibodies M2 subtype are not analyzed due to the small sample size (n<3)
Table 2. Initial clinical presentations of CS patients

| Initial clinical presentation                  | Patients (%) | Initial clinical presentation leading to first clinical visit | Patients (%) |
|-----------------------------------------------|--------------|-------------------------------------------------------------|--------------|
| Fever                                         | 6 (37.5%)    | 6 (100%)                                                   |              |
| Fever + abdominal pain                        | 3 (18.75%)   | 3 (100%)                                                   |              |
| Abdominal distention                          | 8 (50%)      | 5 (62.5%)                                                  |              |
| Fever + abdominal distention                   | 1 (6.25%)    | 1 (100%)                                                   |              |
| Gastrointestinal bleeding                      | 1 (6.25%)    | 1 (100%)                                                   |              |
| Fatigue                                       | 1 (6.25%)    | 1 (100%)                                                   |              |
| Other                                         | 1 (6.25%)    |                                                            |              |

* % of patients in whom the very initial clinical presentation led to the first clinical visit.

# The patient went to hospital due to upper respiratory infection and was found to have splenomegaly.

Table 3. Imaging studies of CS patients.

| Image modality | Patients examined before diagnosis | Average times examined per patient | Patients diagnosed by this modality | Accuracy |
|----------------|-----------------------------------|-----------------------------------|------------------------------------|----------|
| US             | 16                                | 1.9                               | 4                                  | 25%      |
| CT             | 13                                | 1.3                               | 9                                  | 69.2%    |
| MRCP           | 12                                | 0.8                               | 10                                 | 83.3%    |
| Any Imaging    | 16                                | 4.4                               | 14                                 | 87.5%    |

CT: computed tomography, MRCP: magnetic resonance cholangiopancreatography, US: ultrasound

Table 4. Sensitivity of different signs by US in diagnosing CS patients.

| Patients/Patients tested | Proportion |
|--------------------------|------------|
| Splenomegaly             | 15/16      | 93.8%     |
| Diffuse hepatic lesions  | 10/16      | 62.5%     |
| Hepatic cysts            | 10/16      | 62.5%     |
| Diffuse hepatic lesions + splenomegaly | 10/16 | 62.5%     |
| Hepatic cysts + splenomegaly | 9/16 | 56.3%     |
| Renal cysts              | 8/16       | 50%       |
| Renal cysts + splenomegaly | 8/16 | 50%       |
| Hepatic cysts + renal cysts + splenomegaly | 6/16 | 37.5%     |

US: ultrasound

Figures
Figure 1

Diagnostic timelines of 16 CS patients. Important time points including onset of clinical presentation, first clinical visit, and diagnosis are depicted for each CS patient along the timeline. The course of the disease was divided into three phases: phase 1 (blue), defined as no proof of complication of portal hypertension (i.e., hypersplenism); phase 2 (purple), defined as discovered complication of portal hypertension without gastrointestinal variceal bleeding; and phase 3 (red), defined as at least one recorded variceal bleed. Imaging modalities and/or biopsy used before diagnosis are marked along the timelines. US: ultrasonography; CT: computed tomography; CT+C: computed tomography with contrast; MRI: magnetic resonance imaging; MRCP: magnetic resonance cholangiopancreatography; PET/CT: positron emission tomography/computed tomography.
Figure 2

CT scan of a CS patient revealing multiple dilatations of intrahepatic bile ducts (arrow) and tiny dots of strong contrast within, which is the central dot sign (arrowhead).
Figure 3

MRCP in a CS patient showing dilatation of intrahepatic bile ducts.