CASE REPORT

REVISED Case Report: Intrahepatic cholestasis: a diagnostic dilemma

[version 2; peer review: 1 approved, 3 approved with reservations]

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Abstract

Cholestasis is an impairment of bile formation or bile flow. The mechanisms of cholestasis can be broadly classified into intrahepatic and extrahepatic. Most of the time, etiology can be determined with proper history, physical examination, and diagnostic testing including laboratory and imaging tests. This is a case report of a patient with severe cholestasis who underwent extensive evaluation to determine the etiology of intrahepatic cholestasis.

This Case Report details a 28-year-old male who presented with seven days' history of yellowish discoloration of eyes, the passage of dark-colored urine, generalized body itching, and the passage of clay-colored stool. The patient had no similar episode in the past. Laboratory investigations showed unconjugated hyperbilirubinemia and increased alkaline phosphatase. Magnetic resonance cholangiopancreaticography was unremarkable and liver biopsy was suggestive of cholestatic pattern and negative for acute hepatitis. The bilirubin level started decreasing after a month.

The etiology of intrahepatic cholestasis remained unknown. Genotyping could not be done due to limited available resources. It may have helped to diagnose familial hepatocellular cholestasis such as benign recurrent intrahepatic cholestasis (BRIC) and progressive familial intrahepatic cholestasis. Gamma-glutamyl transferase is normal or mildly elevated in patients with BRIC. A similar picture was seen in our case as well. If the patient presents again with similar symptoms and findings, we can consider the diagnosis of BRIC.

Open Peer Review

Approval Status ? ? ? ✓

	1	2	3	4
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version 1 24 May 2023	? view	? view		

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords
Cholestasis, Intrahepatic cholestasis, BRIC

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Author roles: Acharya U: Data Curation, Resources, Writing – Original Draft Preparation; **Panthi RC**: Resources, Writing – Original Draft Preparation; **Shrestha R**: Resources, Supervision, Writing – Review & Editing; **Pandey B**: Supervision, Writing – Review & Editing; **Adhikari S**: Supervision, Writing – Review & Editing; **Koirala J**: Supervision, Writing – Review & Editing; **Basnyat B**: Supervision, Writing – Review & Editing

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First published: 24 May 2023, **8**:226 https://doi.org/10.12688/wellcomeopenres.19381.1

REVISED **Amendments from Version 1**

The revised version of this case report includes revisions made based on the expert comments of the peer reviewers. Details have been added to the case presentation to improve clarity. New figure has been added to show the trend of ALP change during hospital stay and follow-up as was suggested by the reviewers.

Any further responses from the reviewers can be found at the end of the article

Introduction

Cholestasis is an impairment of bile formation or bile flow. Patients with cholestasis present with fatigue, pruritus, and jaundice. Cholestasis may be intrahepatic or extrahepatic[1]. The presentation of intrahepatic cholestasis and associated biochemical abnormalities may mimic biliary obstruction and can generate diagnostic confusion. Causes of intrahepatic cholestasis include primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), drugs and toxins, sepsis, malignancy, granulomatous liver disease, intrahepatic cholestasis of pregnancy, viral hepatitis, alcoholic hepatitis, genetic disorders, total parenteral nutrition associated cholestasis, graft versus host disease, post liver transplant cholestasis, etc[2,3].

Clinically, cholestatic disorder manifests as jaundice, pruritus and symptoms secondary to malabsorption of fat and fat-soluble vitamins[4]. Biochemical markers of cholestasis include predominant elevation of serum alkaline phosphatase (ALP) relative to aminotransferases. Intrahepatic cholestatic disorders can be categorized histologically as infiltrative, those associated with injury to cholangiocytes within intrahepatic bile ductules, and those in which major histologic changes are not evident[3].

The diagnosis of intrahepatic cholestasis is made after imaging rules out extrahepatic biliary obstruction. Depending on the clinical situation, evaluation requires different serological studies in order to determine etiology, and sometimes it needs to be confirmed with a liver biopsy[5,6]. Here we report a case of a patient who presented in a tertiary care hospital in Nepal in which the etiology of intrahepatic cholestasis remained unknown even after extensive workup.

Case report

A 28-year-old male, Newar by ethnicity, from central Nepal and journalist by occupation, previously healthy, presented with seven days' history of yellowish discoloration of eyes, passage of dark-colored urine, generalized body itching, and passage of clay-colored stool. The patient denied history of fever, abdominal pain, or viral prodrome. He used to consume alcohol on social occasions with the last intake around one month prior to the illness. He did not have a history of intake of any medications including herbal supplements and had not previously had biliary tract surgery. There was no family history of jaundice or liver disease. Physical examination revealed icterus and excoriation marks all over the body. Other examination findings were unremarkable. Initial laboratory investigations revealed total bilirubin of 30.1 mg/dl (Reference: 0.4-1), direct bilirubin 19.3 mg/dl (Reference: 0.04-1), aspartate aminotransferase (AST) 14 units/liter (Reference: 0-37), alanine aminotransferase (ALT): 21.0 units/Liter (Reference: 5-35), alkaline phosphatase (ALP): 418 units/liter (Reference: 53-125), and gamma-glutamyl transferase (GGT):17 units/liter (Reference: 8-61). Serum Albumin was 4.8 g/dl (Reference: 3-5), prothrombin time (PT): 14.7 (Reference: 11-14), international normalized ratio (INR): 1.05 (Reference: 1.0-1.3). Serological markers for hepatitis A, hepatitis B, hepatitis C, hepatitis E, and human immunodeficiency virus (HIV) were negative.

The patient was initially admitted to the surgical ward for evaluation of obstructive jaundice. Ultrasound of the abdomen done soon after admission showed no abnormality in the biliary tree. Contrast-enhanced computed tomography (CECT) of the abdomen (done on day three) and magnetic resonance cholangiopancreatography (MRCP) (done on day four) also did not show any abnormality in the biliary tract, pancreas, and peripancreatic region. After ruling out extrahepatic causes with imaging studies, the patient was shifted to the medical ward for further evaluation of intrahepatic cholestasis. Various investigations to determine the etiology of intrahepatic cholestasis were done including thyroid function tests, antinuclear antibody (ANA), liver kidney muscle-1 (LKM-1) antibody, anti-smooth muscle antibody (ASMA), antimitochondrial antibody (AMA), immunoglobulin G (IgG) -total, carcinoembryonic antigen (CEA), carbohydrate antigen 19.9 (CA-19.9), alpha-fetoprotein (AFP), serum ceruloplasmin, 24-hour urinary copper and iron profile; the results of which did not reveal the etiology of intrahepatic cholestasis. Blood culture did not reveal any growth; serologies for brucellosis, leptospirosis, and scrub typhus were all negative. Malaria antigen was negative. Because of the persistent pruritus, the patient was managed with ursodeoxycholic acid 15 mg/kg/day in 2 divided doses, cholestyramine 4 g twice daily and, levocetirizine 5 mg once daily. As fat-soluble vitamins are low in cholestasis, empiric supplementations were done with cholecalciferol oral 60000 IU once and Inj. vitamin K 10mg iv once. The pruritus decreased after the treatment. The trends of bilirubin and ALP during his illness have been shown in Figure 1 and Figure 2 below. GGT was normal throughout, while ALT and AST had increased during the hospital stay (up to 91 and 127 U/L) which later normalized until discharge.

During the hospital stay, he developed hospital-acquired pneumonia which was managed with Inj. piperacillin-tazobactam 4.5g IV thrice daily for seven days, and the patient recovered from pneumonia. He also developed acute kidney injury which got resolved with intravenous fluids. A liver biopsy was performed. The patient's symptoms gradually improved, and his bilirubin also started to decrease gradually. So, he was discharged after 34 days of hospital stay, with advice to follow up with liver biopsy report. On follow-up seven days after discharge, a histopathology report of liver biopsy showed bile stasis with minimal inflammatory cell infiltration, suggestive of

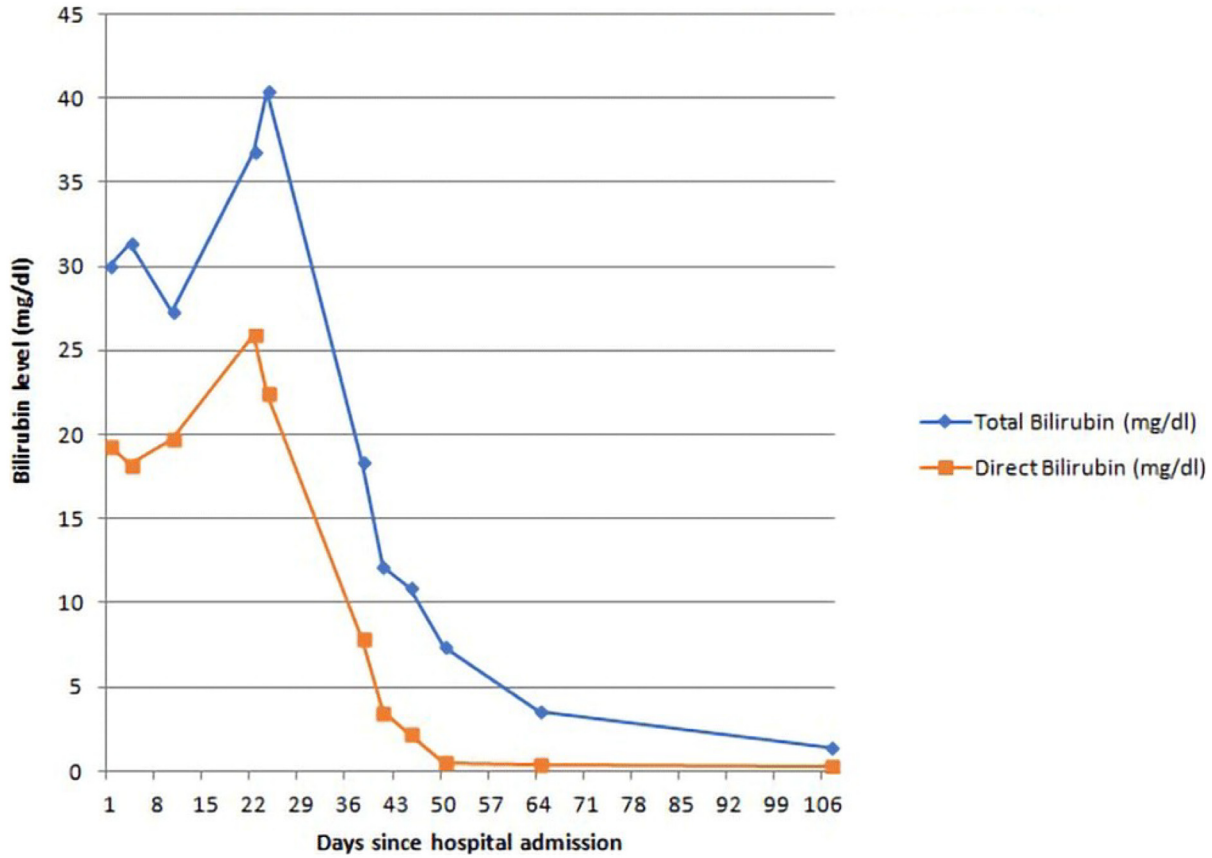

Figure 1. Trend in bilirubin level of the patient.

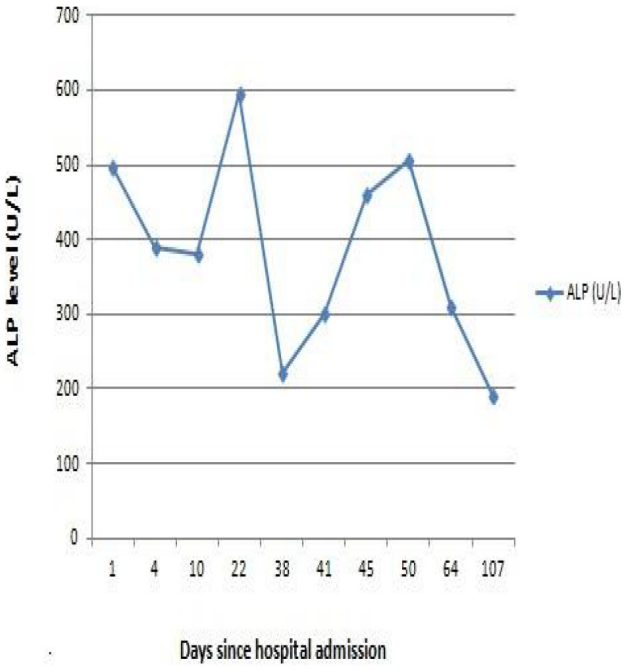

Figure 2. The trend in ALP level of the patient.

cholestatic pattern and negative for acute hepatitis. However, the etiology of intrahepatic cholestasis still remained unknown. The patient was regularly followed. His bilirubin normalized in about 8 weeks and ALP normalized in about 16 weeks after the onset of illness.

Discussion

Intrahepatic cholestasis is considered once the extrahepatic cholestasis is ruled out by imaging modalities[4], as in our case in which CECT abdomen and MRCP were normal. On the evaluation of the etiology of intrahepatic cholestasis, our patient did not have a history of any drug intake or significant alcohol consumption. Serology for viral hepatitis and autoimmune hepatitis were negative. Test results were also negative for primary biliary cirrhosis and primary sclerosing cholangitis as AMA and MRCP were normal, respectively. Liver biopsy ruled out small duct PSC. Serum ceruloplasmin, slit-lamp exam for Kayser Fleischer ring, and 24-hour urinary copper were negative for Wilson`s disease. Iron studies did not suggest hemochromatosis as the cause of intrahepatic cholestasis. Genetic testing should also be considered such as mutations in the hepatobiliary transporters ATP8B1, ABCB11 and ABCB4 in the evaluation of familial hepatocellular cholestasis like progressive familial intrahepatic cholestasis (PFIC) or benign recurrent

intrahepatic cholestasis (BRIC). However, genetic testing, though a gold standard test, was not done in our case because of the limited available resources.

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of disorders, characterized by defective secretion of bile acids or other components of bile. PFIC is unlikely in our case as these disorders usually present during infancy or childhood, and are associated with growth failure and progressive liver disease.

Benign recurrent intrahepatic cholestasis (BRIC) is characterized by recurrent cholestatic episodes. Patients present with this disease for the first time at a young age (usually at teens or twenties). The frequency of attacks can vary, ranging from once in a few months to once in a decade. During the attacks, the patients present with malaise, anorexia, pruritus, weight loss, jaundice, and malabsorption. Laboratory tests reveal biochemical evidence of cholestasis (conjugated hyperbilirubinemia, raised ALP). GGT is normal or mildly elevated in patients with BRIC. A similar picture was seen in our case as well.

There was one factor which made the diagnosis of BRIC challenging in our case. BRIC is a recurring disease. But our patient had no similar episode in the past. The diagnosis of BRIC could not be ascertained due to it being the first presentation. Genetic testing, if performed, could have led to the diagnosis of BRIC in just one attack.

There is no specific treatment for BRIC. Bile acid sequestrants such as Cholestyramine, opioid antagonists such as Naltrexone, antihistamines, Rifampin, Ursodeoxycholic acid, Sertraline, and nasobiliary drainage may improve pruritus in a patient with BRIC.

Liver biopsy is important in the workup of patients with cholestatic jaundice who have normal imaging and no other obvious etiology[1]. However, it may not be adequately sensitive, and may have complications such as bleeding. Although histological examination of liver tissue confirmed the diagnosis of intrahepatic cholestasis, the cause still remained unanswered in this case.

If the patient presents again with similar symptoms and findings, we can consider the diagnosis of BRIC. Genotyping would be helpful in reaching the diagnosis.

Informed consent

Written informed consent was taken from the patient before submission.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

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PubMed Abstract | Publisher Full Text

Open Peer Review

Current Peer Review Status: ? ? ? ✓

Version 2

Reviewer Report 25 November 2024

https://doi.org/10.21956/wellcomeopenres.23554.r110997

✓ **Bagus Setyoboedi**
Universitas Airlangga, Surabaya, Indonesia
Rendi Aji Prihaningtyas
Child Health, Universitas Airlangga (Ringgold ID: 148005), Surabaya, East Java, Indonesia

This case report has a clear backgdound. The case is described in detail and a detailed examination has been conducted. Application in clinical practice is easy but requires costly investigations.Liver function test charts such as AST and ALT can be included as well as GGT evaluation to further reveal the trend of treatment success.

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: hepatology

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 23 August 2024

https://doi.org/10.21956/wellcomeopenres.23554.r92307

?

Tai Ren
Shanghai Jiao Tong University, Shanghai, China
Yang Li
Department of Biliary-Pancreatic Surgery, Renji Hospital, Shanghai, China

The authors reported an interesting case of severe intrahepatic cholestasis. The laboratory and imaging results provide logical and necessary information to exclude a extrahepatic source. The comprehensive serological results did not support other liver diseases but indicate a possible genetic origin. In addition to the trends in TB, DB, and ALP, it would be of interest to show the trend in GGT during the process. Though a confirmative genetic assessment was not performed, I agree that BRIC is likely to be the diagnosis. The case is in general well-presented. Some language issues may require further revision (eg. two verbs in "The diagnosis of intrahepatic cholestasis is made after imaging rules out extrahepatic biliary obstruction.").

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Hepatobiliary diseases, perinatal care, epidemiology

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Version 1

Reviewer Report 04 December 2023

https://doi.org/10.21956/wellcomeopenres.21468.r69965

?

Kate Lynch
Royal Adelaide Hospital Adelaide, Adelaide, Australia

It would have been useful to know if the serologies mentioned were completely normal or just not "confirming" a disease. ANCA may have also been useful in the setting of small duct-PSC, where it can be patchy.

The normal GGT with raised bilirubin and ALP, and the lack of abdominal pain, should be brought out strongly. When one sees a normal GGT with cholestasis, one automatically thinks of the PFIC and BRIC disorders.

I disagree that the patient's age of presentation makes the diagnosis confusing. I often diagnose it in early adulthood. It may not have been evident previously as was subclinical, where this was a severe flare. Were there any prior liver function tests available to evaluate?

I agree the most likely diagnosis is BRIC. We see this more commonly in women when they start using hormonal therapy and/or become pregnant, and cases can be severe like this. Option can also include nasobiliary drainage if symptoms not responding to UDCA/colestyramine/rifampicin. Interesting case though.

Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Autoimmune liver disease, cholestatic liver diseases, inflammatory bowel disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 16 Mar 2024

Sudeep Adhikari

Thank you for the comments. Below is the detailed point by point response to your comments.

Q- It would have been useful to know if the serologies mentioned were completely normal or just not "confirming" a disease. ANCA may have also been useful in the setting of small duct-PSC, where it can be patchy.
A- ANCA was not done in our case. However other serologies mentioned in the manuscript were completely normal.

Q- The normal GGT with raised bilirubin and ALP, and the lack of abdominal pain, should be brought out strongly. When one sees a normal GGT with cholestasis, one automatically thinks of the PFIC and BRIC disorders.
A- Thank you for the comment.

Q- I disagree that the patient's age of presentation makes the diagnosis confusing. I often diagnose it in early adulthood. It may not have been evident previously as was subclinical, where this was a severe flare. Were there any prior liver function tests available to evaluate?
A- We agree with your comment. Changes have been made in the manuscript. There was no prior LFT done in this case.

Q- I agree the most likely diagnosis is BRIC. We see this more commonly in women when they start using hormonal therapy and/or become pregnant, and cases can be severe like this. Option can also include nasobiliary drainage if symptoms not responding to UDCA/colestyramine/rifampicin. Interesting case though.
A- Thank you for the comment.

Competing Interests: No competing interests were disclosed.

Reviewer Report 04 December 2023

https://doi.org/10.21956/wellcomeopenres.21468.r69971

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Holmfridur Helgadottir

Haraldsplass Deaconal Hospital (HDS), Bergen, Norway

This case of severe intrahepatic cholestasis is interesting, the absence of abnormality on imaging and exclusion of other causes of liver disease is important when considering genetic liver disease. When the laboratory tests show profound cholestasis and normal GGT that raises suspicion for BRIC and other forms of familial intrahepatic cholestasis. Normal or minimally elevated GGT is the hallmark of BRIC. However, in this case, although the patient had extensive evaluation the genetic test is missing, and when that is not done the patient needs to have at least two attacks of jaundice separated by a symptom free interval to meet the diagnostic criteria.

We have > 100 BRIC cases reported worldwide, could this be the first case in Nepal?

Introduction:

- It is not correct to use bile acids in this sentence/statement: *"Clinically, cholestatic disorder manifests as jaundice and pruritus from the retention of bile acids in the blood..."*
  The jaundice is a manifestation of hyperbilirubinemia and the pathogenesis of pruritus in cholestatic disorders is complex; various candidate pruritogens have been studied and bile acids is just one of many.

- Jaundice is also not a biochemical marker, it is a clinical manifestation of cholestasis.

- One sentence has two period marks: "*out extrahepatic biliary obstruction. .*"

Case report:

- Ref. values are provided for laboratory results, except for prothrombin time.

- When was CT taken, at admission or later (please provide day number during admission)? CT scan may identify gallstones but it's usually not as effective as the ultrasound – in this case it is important to rule out gallstones that could have passed through (important ddx).

- Was there not done abdominal ultrasound during admission to the hospital?

- Was MRI done early in admission (please provide day number during admission)?

- How was medical treatment chosen? What was the indication for the treatment of choice? Was pruritus' the indication for medical treatment? And can you provide any information on the effect the medications had on the symptom?

- Can you provide UDCA dose in mg/kg for the case?

- What was the indication for K vitamin injection, was there rise in INR value during hospital stay?

- The liver biopsy, was the histology demonstrating centrilobular cholestasis?

Figure 1:

- The figure only shows bilirubin and DB. It would be interesting to also show the

changes/curve for ALP.

- Did GGT stay normal the whole time?

- Was there any change in ALT and AST – that is sometimes seen in BRIC attacks.

Discussion:

- It is true that this could be a BRIC attack, however PFIC is very unlikely. PFIC typically presents in early life, rarely in early adulthood – this section can be shortened in the discussion.

- BRIC does not usually present in infancy to late adulthood – in most cases the first attack occurs during the patient's teens or twenties. This should be corrected. The diagnosis has been made in infancy in families with a history of BRIC.

- Here the attack lasted a month and also bilirubin started decreasing after a month. How was the duration of the attack counted and how long was the admission time (hospital stay)?

- How long was the duration until all laboratory results were normal? In the literature the mean duration is approximately 12 weeks. I would also recommend to count the duration from the first sign/symptom.

- The attacks can have complications, such as pancreatitis or kidney failure, was there elevation of amylase, lipase or creatinine?

- The treatment choices for BRIC attacks should be mentioned in discussion.

- The etiology of the case remained unknown – the diagnosis of BRIC can be confirmed by genetic testing after just one attack and that should be stated as the gold standard in the discussion. Before the genetic testing the diagnosis was more difficult, and patients had to have a minimum of two attacks of jaundice separated by intervals of weeks to years without any symptoms or cholestasis.

- I would recommend to get genetic testing, which is the gold standard for diagnosis as well as for the classification of the disease. This could also be of importance to decide for further follow-up and the choice of treatment of the next attack.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cholestatic liver diseases and cholestatic pruritus

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 16 Mar 2024

Sudeep Adhikari

Thank you for your comments. Below is the detailed point by point response to your comments.

Introduction:
Q- It is not correct to use bile acids in this sentence/statement: “Clinically, cholestatic disorder manifests as jaundice and pruritus from the retention of bile acids in the blood…”
A- Suggested changes have been made in the manuscript.

Q- The jaundice is a manifestation of hyperbilirubinemia and the pathogenesis of pruritus in cholestatic disorders is complex; various candidate pruritogens have been studied and bile acids is just one of many.
A- Suggested changes have been made in the manuscript.

Q- Jaundice is also not a biochemical marker, it is a clinical manifestation of cholestasis.
A- Suggested changes have been made in the manuscript.

Q- One sentence has two period marks: “out extrahepatic biliary obstruction. .”
A- Suggested changes have been made in the manuscript.

Case report:
Q- Ref. values are provided for laboratory results, except for prothrombin time.
A- Suggested changes have been made in the manuscript.

Q- When was CT taken, at admission or later (please provide day number during admission)? CT scan may identify gallstones but it's usually not as effective as the ultrasound – in this case it is important to rule out gallstones that could have passed through (important ddx). Was there not done abdominal ultrasound during admission to the hospital? Was MRI done early in admission (please provide day number during admission)?
A- CT scan was done on day 3, MRCP on day 4. Ultrasound of the abdomen was done soon after admission which showed no abnormality.

Q- How was medical treatment chosen? What was the indication for the treatment of choice? Was pruritus' the indication for medical treatment? And can you provide any information on the effect the medications had on the symptom?
A- Medical treatment was given to relieve patient of pruritus. After the treatment, pruritus was improved. Jaundice was also reduced.

Q- Can you provide UDCA dose in mg/kg for the case?
A- UDCA was given at the dose of 15 mg/kg/day.

Q- What was the indication for K vitamin injection, was there rise in INR value during hospital stay?
A- Vitamin K injection was given as empiric treatment for possible reduced fat soluble vitamin level due to cholestasis. However, INR was normal during hospital stay.

Q- The liver biopsy, was the histology demonstrating centrilobular cholestasis?
A- There was no centrilobular cholestasis seen in biopsy.

Q- Figure 1: The figure only shows bilirubin and DB. It would be interesting to also show the changes/curve for ALP.
A- ALP trend figure has been added.

Q- Did GGT stay normal the whole time?
A- GGT was normal.

Q- Was there any change in ALT and AST – that is sometimes seen in BRIC attacks.
A- There was slight increment in values of ALT and AST. Discussion:

Q- It is true that this could be a BRIC attack, however PFIC is very unlikely. PFIC typically presents in early life, rarely in early adulthood – this section can be shortened in the discussion.
A- Suggested changes have been made in the manuscript.

Q- BRIC does not usually present in infancy to late adulthood – in most cases the first attack occurs during the patient's teens or twenties. This should be corrected. The diagnosis has been made in infancy in families with a history of BRIC.
A- Suggested changes have been made in the manuscript.

Q- Here the attack lasted a month and also bilirubin started decreasing after a month. How was the duration of the attack counted and how long was the admission time (hospital stay)? A- Hospital stay was 34 days.

Q- How long was the duration until all laboratory results were normal? In the literature the mean duration is approximately 12 weeks. I would also recommend to count the duration from the first sign/symptom.
A- His bilirubin normalized in about 8 weeks and ALP normalized in about 16 weeks after the onset of illness.

Q- The attacks can have complications, such as pancreatitis or kidney failure, was there elevation of amylase, lipase or creatinine?
A- He had developed AKI during hospital stay, but no pancreatitis.

Q- The treatment choices for BRIC attacks should be mentioned in discussion.
A- Suggested changes have been made in the manuscript.

Q- The etiology of the case remained unknown – the diagnosis of BRIC can be confirmed by genetic testing after just one attack and that should be stated as the gold standard in the discussion. Before the genetic testing the diagnosis was more difficult, and patients had to have a minimum of two attacks of jaundice separated by intervals of weeks to years without any symptoms or cholestasis.
A- Suggested changes have been made in the manuscript.

Q- I would recommend to get genetic testing, which is the gold standard for diagnosis as well as for the classification of the disease. This could also be of importance to decide for further follow-up and the choice of treatment of the next attack.
A- Genetic testing is not available in our setup so could not be done. It has been acknowledged in the manuscript.

Competing Interests: No competing interests were disclosed.