**Benign Recurrent Intrahepatic Cholestasis (BRIC): A Case Report in Morocco**

**Abstract:** Benign recurrent intrahepatic cholestasis (BRIC) is a rare autosomal recessive inherited disorder characterized by intermittent episodes of severe cholestatic jaundice. After researching the main causes of cholestasis: viral hepatitis, drug and toxic origin, and also eliminate a biliary obstructive cause. Benign recurrent intrahepatic cholestasis (BRIC) is characterized by repeated self-limited episodes of severe pruritus and jaundice that last from several weeks to months. Diagnosis is based on a compatible clinical presentation, laboratory parameters and histology with exclusion of other causes of cholestasis and confirmed by genetic testing. The objective of this clinical case report is to focus on the diagnostic criteria and to recall the main characteristics concerning BRIC in the literature.

**Keywords:** BRIC, intrahepatic cholestasis, jaundice, pruritus.

**INTRODUCTION:**

Benign recurrent intrahepatic cholestasis (BRIC) is a rare autosomal recessive inherited disorder characterized by intermittent episodes of severe cholestatic jaundice. The diagnosis is often delayed, and the patients frequently experience invasive diagnostic procedures without any conclusions. BRIC is an exclusion diagnosis, after researching the main causes of cholestasis: viral hepatitis, drug and toxic origin, and also eliminate a biliary obstructive cause. After a negative investigation, we can evoke BRIC.

Benign recurrent intrahepatic cholestasis (BRIC) is characterized by repeated self-limited episodes of severe pruritus and jaundice that last from several weeks to months. Although each BRIC attack can be associated with significant morbidity, progressive liver injury and cirrhosis do not occur. A brief review of the disorder is presented. The objective of this clinical case is to report a new observation, to focus on the diagnostic criteria and to recall the main characteristics concerning BRIC in the literature. The objective of this clinical case is to report a new observation, to focus on the diagnostic criteria and to recall the main characteristics concerning BRIC in the literature.

**Observation**

A 34-years-old Moroccan woman presented to our unit in January 2020 with history of pruritus for one month and jaundice for Twenty days. The pruritus was severe, generalized, and worse at night. She also experienced weight loss, asthenia, loss of appetite, dyspepsia, and right upper quadrant pain associated with nonbilious vomiting.

Her urine was dark and his stools loose, fatty, and uncolour. She had no fever, arthralgia, myalgia, or rash. She had no history of viral hepatitis, food or drug allergies, or alcohol or tobacco abuse.

She reported no family history of cholestasis or liver disease. She had a similar episode in 2015, with no specific diagnosis despite a liver biopsy (histology nonspecific intrahepatic cholestasis). The patient reported then a spontaneous improvement after two months without any treatment, pruritus stopped spontaneously, she noted an increase in appetite with resolution of asthenia. Jaundice was the last to resolve after two weeks.

On examination, we found a patient with BMI: 17.7kg/m² with jaundice and excoriations marks on his body.
There were no stigmata of chronic liver disease. Abdominal examination revealed mild right upper quadrant tenderness with a negative Murphy’s sign, a normal liver span, and no clinically detectable ascites.

Her liver function tests revealed a biologic cholestasis with markedly elevated total bilirubin (32N), predominantly direct (55N). Alkaline phosphatase was elevated to four times the upper limit of normal, but gamma glutamyl transference was normal, as were the transaminases. Prothrombin time was 76%. Serology for hepatitis A, B, and C and HIV 1&2 were negative.

An abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP) both revealed a normal liver with normal biliary and pancreatic ducts, with atrophic sclerotic gallbladder. The Echo endoscopy found a gallbladder lithiasis with empty undilated principal bile duct.

Liver biopsy found a preserved normal liver architecture with mononuclear inflammatory elements, the hepatocytes had moderate intrahepatic cholestasis predominantly in the centrilobular zone with biliary thrombi (Fig. 1).

Based on clinical, laboratory tests, and histologic findings, she was diagnosed with BRIC as per the criteria proposed by Luketic and Shiffman (Table 1).

She had AUC 15mg/kg /Day, and for pruritus: Sertraline 100 mg /Day with rapid resolution of symptoms and improvement in biochemical markers, and programmed for cholecystectomy.

**DISCUSSION:**

BRIC was first described in two patients from England (Summerskill, W. H. J., & Walsh, J. M. 1959). Subsequent reports have shown that the disorder occurs in patients from Northern and Mediterranean Europe, Africa, North and South America, and Japan (Brenard, R. et al., 1989; & Schapiro, R.H., & Isselbacher, K.J. 1963). Although most of the described cases are sporadic, the discovery that a family history of cholestasis is present in up to half the affected patients led early to genetic studies showing BRIC to be an autosomal recessive disorder (Kuhn, H.A. 1963; & Tygstrup, N. 1960). More recently, mapping studies have placed the defective gene on the long arm of chromosome 18 (De Koni ng, T. J. et al., 1995; & Houwen, R.H. et al 1994).

The first attack of pruritus and jaundice typically occurs during the patient’s teens or twenties (Brenard, R. et al., 1989 ; De Pagter, A. G. F. et al., 1976 ; & Tang, X. et al., 1996). The duration and number of attacks varies widely from person to another. Each attack can last from 2 weeks to 18 months. The mean duration is approximately 3 months (Brenard, R. et al., 1989). The reported male predominance (Brenard, R. et al., 1989 ; De Pagter, A. G. F. et al., 1976 ; & Lesser, P. 1973 ) may result from under diagnosis of BRIC among women the two most common features of BRIC, intense pruritus and jaundice, have been misattributed to pregnancy or to the use of oral contraceptives in many women (Brenard, R. et al., 1989 ; De Pagter, A. G. F. et al., 1976).

In our case, the patient had a similar episode that spontaneously regressed.

The main manifestations are asthenia and jaundice for which research has not found an evident cause, with negative viral serologies, normal metabolic parameters and imagery not finding any biliary obstacle. the
research for the genetic mutations is not essential for the diagnosis, if all arguments has been reunited.

**Signs and symptoms**

The signs and symptoms of BRIC are summarized in Table 1. Pruritus and jaundice are hallmarks of the disease. Pruritus often appears as a prodrome and precedes jaundice by 2 to 4 weeks (Tygstrup, N. & Jensen, B. 1969; Brenard, R. et al., 1989; Tygstrup, N. 1960; & Summerskill, W.H.J. 1965). One fourth of patients may never develop pruritis while in others the scleral icterus is barely noticeable (Brenard, R. et al., 1989).

Other common symptoms include Steatorrhea caused by fat malabsorption and anorexia can lead to significant weight loss during prolonged episodes of cholestasis (Tygstrup, N. & Jensen, B. 1969; & WILLIAMS, R. et al., 1964).

Although the symptom complex varies from patient to patient, it remains remarkably consistent in an individual patient during recurrent attacks. In contrast, other clinical features of chronic cholestatic liver diseases such as splenomegaly, spider nevi, palmar erythema, and xanthelasma are universally absent (Tygstrup, N. & Jensen, B. 1969; Summerskill, W.H.J. 1965; & WILLIAMS, R. et al., 1964).

Improvement in appetite often heralds the resolution of a BRIC attack. This improvement is followed by the sudden and complete resolution of pruritus and the gradual resolution of jaundice (Tygstrup, N., & Jensen, B. 1969).

**Laboratory findings and liver histology**

Laboratory findings during episodes reveal an elevated total bilirubin, which is predominantly direct.

Alkaline phosphatase is always elevated, sometimes markedly. Transaminases are normal or mildly elevated but can also be markedly elevated (Brenard, R. et al., 1989; & Nakamuta, M. et al., 1994). Early ALT rise that eventually resolves has also been described, a trend seen in our patient during his second episode (Velimir, A. et al., 2004).

The characteristic hallmark of BRIC and other forms of familial intrahepatic cholestasis that separates these disorders from other causes of intrahepatic cholestasis is the g-glutamyl transferase (GGT) level, which either remains normal or is only minimally elevated, as seen in this patient.


Less common findings include pericentral hepatocellular degeneration; hepatocyte necrosis and inflammation in areas lacking bile pigment; focal lobular mononuclear cell infiltrate; portal inflammation consisting of mononuclear cells and occasionally eosinophils; cholangiolar proliferation; and lobular changes suggestive of cholate injury. These changes resolve completely between episodes (Luketic, V. A., & Shiffman, M. L. 2004; & De Koning, T. J. et al., 1995).

Diagnosis is based on the criteria proposed by Luketic and Shiffman (Luketic, V. A., & Shiffman, M. L. 2004) (Table 1) with genetic testing for mutations used as a confirmation (Folvik, G. et al., 2012).

**Table 1:** Diagnostic criteria for BRIC (Luketic, V. A., & Shiffman, M. L. 2004)

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<tr>
<th>Diagnostic criteria for BRIC (LUKETIC and SHIFFMAN, 2004)</th>
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<td>• At least two attacks of jaundice separated by a symptom-free interval lasting several months to years</td>
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<td>• Laboratory values consistent with intrahepatic cholestasis GGT either normal or only minimally elevated</td>
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<td>• Severe pruritus secondary to cholestasis</td>
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<td>• Liver histology demonstrating centrilobular cholestasis</td>
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<td>• Normal intra- and extrahepatic bile ducts by cholangiography. Absence of factors known to be associated with cholestasis (i.e, drugs and pregnancy)</td>
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**Treatment**

Because the cause of BRIC is unknown, specific treatment that could either prevent or limit the duration of attacks is not available. The key to treatment is symptom relief until there is spontaneous resolution of pruritus and other symptoms (Velimir, A. et al., 2004). High dose fat-soluble vitamins should be supplemented to prevent deficiency during prolonged episodes. Bile acid sequestrants such as cholestyramine, opioid antagonists, and ursodesoxycholic acid may reduce pruritus but not the duration of episodes (European Association For The Study Of The Liver, 2009; & European Association For The Study Of The Liver, 2009). Rifampicin, plasmapheresis, and endoscopic nasobiliary drainage have all been shown to relieve symptoms and shorten episodes (Folvik, G. et al., 2012; & Velimir, A. et al., 2004). Rifampicin is safe and effective in reducing pruritus associated with chronic cholestasis (Khanna, S., & Singh, P. 2006). Our case shows the difficulties faced in diagnosing such a rare disease.
CONCLUSION

In conclusion BRIC is a rare cause of chronic cholestasis, main cholestatic disease’s should run out before confirming BRIC diagnosis by Luketic and Shiffman criteria’s. The research for the genetic mutations is not essential for the diagnosis and the treatment is symptomatic.

REFERENCES:


