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CASE REPORT | BILIARY

Hyperthyroidism as a Potential Trigger for Benign Recurrent Intrahepatic Cholestasis

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ABSTRACT

Benign recurrent intrahepatic cholestasis (BRIC) is a rare genetic disease often causing episodes of jaundice since childhood. Its triggering factors are still unknown. Hyperthyroidism solely is an infrequent cause of jaundice, and it was never described in association with BRIC. In this article, we reported a woman presenting with a new episode of BRIC and was found to have concomitant hyperthyroidism in the absence of any other potential trigger factor. We conclude that hyperthyroidism may trigger cholestasis in patients with BRIC.

INTRODUCTION

Benign recurrent intrahepatic cholestasis (BRIC) is a rare genetic disorder of unknown prevalence. In 1959, it was reported for the first time by Summerskill and Walshe who described 2 patients with a repeated self-limited episode of pruritus and jaundice starting before the third decade of life and lasting for several months.[1] During these episodes, the patient mainly presents with isolated conjugated hyperbilirubinemia and cholestatic finding on liver biopsy. BRIC is principally transmitted in an autosomal recessive manner and associated with mutations of ATP8B1 (FIC1) and ABCB11 (BSEP) genes leading to BRIC type 1 and 2, respectively.[2]

To our knowledge, more than 200 cases of BRIC have been reported to date. Nevertheless, thyroid dysfunction was never reported in association with BRIC. In this study, we report for the first time a case of concomitant BRIC and hyperthyroidism.

CASE REPORT

A 37-year-old woman, known to have BRIC, presented in February 2017 with a 2-month history of pruritus, followed by jaundice, vomiting, and severe epigastric pain. She had experienced 7 similar episodes in her life, occurring at the ages of 3 months and 6, 12, 18, 20, 33, and 35 years. Her sixth and seventh episodes were preceded by pneumonia and pregnancy, respectively. However, the patient's previous medical data lacked any finding that could associate the other episodes with a specific trigger. Each of these episodes lasted for 2 to 5 months before returning to the asymptomatic state. Every episode progressed in the same pattern, starting with pruritus and anorexia, followed by jaundice, diffuse abdominal pain, dark urine, pale stools, and weight loss. She had been on ursodeoxycholic acid since childhood. The patient's parents are first-degree cousins with a negative history of cholestatic diseases in the family.

On physical examination, she had an icteric sclera with diffuse jaundice and epigastric tenderness. Laboratory findings showed a significant increase in total bilirubin (46.9 mg/dL), with 36.3 being direct, and lipase levels (1924 U/L). There was also a mild elevation in aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase (125, 217, and 20 U/L, respectively). Viral serology for hepatitis A, B, and C, cytomegalovirus, and Epstein-Barr virus did not show any acute or chronic infection. In addition, thoracic x-ray, urine, and blood cultures failed to show evidence of any ongoing infection. Thyroid-stimulating hormone level was <0.01 mIU/L with free triiodothyronine and free thyroxine 4 being 1.65 and 13.3 mIU/L, respectively.

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Thyroid scan using technetium-99m pertechnetate (3 mCi) showed a normal-sized, hyperactive thyroid gland with a homogenous uptake of tracer suggesting Graves disease. Abdominal ultrasound and magnetic resonance cholangiopancreatography, performed 2 weeks before her admission, had normal findings. Abdominal computed tomography scan findings were consistent mainly with that of acute interstitial pancreatitis (Figure 1). Transient elastography using FibroScan (Echosens, Paris, France) in time-motion mode was performed and showed a normal value of 3.7 kPa. Antinuclear antibodies, antimitochondrial antibodies, perinuclear antineutrophil cytoplasmic antibodies, and cytoplasmic antineutrophil cytoplasmic antibodies, performed during a previous admission, were all unremarkable. Moreover, genetic testing showed a mutation p. G100E (c.3002 G > A) in the homozygote form at the level of exon 23 of the ATP8B1 gene consistent with BRIC 1.

The patient underwent thyroid ablation by oral radioactive iodine 131 of 20 mCi; then, she was discharged on ursodeoxycholic acid and levothyroxine as a long-term treatment. Her periodic follow-up revealed that bilirubin levels decreased from 49.5 to 36 mg/dL over 3 weeks. However, 3 weeks later, there was an increase in bilirubin to 44 mg/dL along with an increase in thyroid-stimulating hormone level to 63 mIU/L before returning to normal within 10 months.

DISCUSSION

Most episodes of BRIC were not associated with a specific trigger; however, some factors such as pregnancy, viral illnesses, oral contraceptive pills, and others[2–4] were frequently described as triggers for this disease. On the other hand, the occurrence of acute pancreatitis during the presented attack is considered an extrahepatic complication of BRIC 1.[5]

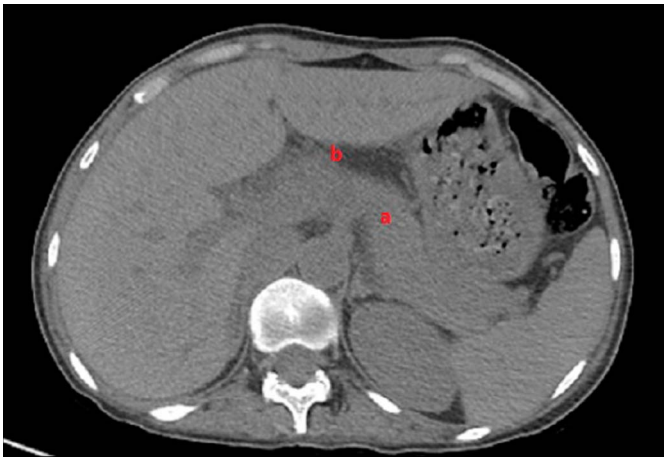

Figure 1. Abdominal computed tomography without contrast demonstrating diffuse enlargement of the pancreas (A) associated with peripancreatic fluid effusion and fat stranding (B) consistent with acute interstitial pancreatitis.

Known as being a rare association, few cases described the occurrence of jaundice secondary to hyperthyroidism.[6] However, hyperthyroidism inducing jaundice in a patient with BRIC was never described. Greenberger et al[7] reported 4 cases of hyperthyroidism associated with jaundice. It pointed out a possible underlying defect in bilirubin metabolism, as seen in Gilbert disease, which has led to jaundice.

Patients presented with cholestasis and hyperthyroidism can be divided into 2 main categories. The first category includes patients having other comorbidities such as congestive heart failure and liver diseases, which may have a prominent role in the pathogenesis of cholestasis.[8] The second one includes patients with no other associated medical condition where hyperthyroidism seems to affect the liver directly. The mechanism of injury in this pure hyperthyroid state is still not well understood.[8] Indeed, liver function and the metabolism of bilirubin are influenced by thyroid hormonal levels.[9,10] One proposition is that the increased thyroxine (T4) level leads to higher oxygen consumption; this, in turn, would lead to an elevation in intrahepatic oxygen-free radicals causing cellular damage.[9] In a more recent experiment, Upadhyay et al demonstrated both in vivo and in vitro that high levels of triiodothyronine activate mitochondrial-dependent pathways, leading to toxicity and dysfunction of liver cells.[11]

Features indicative of endocrine role in the pathogenesis of cholestatic disease were proposed by Raviolo et al in 1991.[6] Although our patient's condition fits most of these criteria, however, there was a mild improvement after thyroidectomy evident by the slight decrease in bilirubin from 49.5 to 44 mg/dL in 2 months. This mild improvement seen after thyroidectomy may have different explanations. First, after thyroid ablation, the patient entered a hypothyroid phase during which the bilirubin level has increased from 36 to 44 mg/dL. Hypothyroidism by itself decreases bile excretion to half and enhances the ratio of conjugated to total bilirubin in the liver and serum, as shown in experimental studies performed on rats.[12] Second, unlike the rapid decrease in bilirubin level reported in previous cases, the mild decrease seen in our case can be related to the presence of ATP8B1 defect. Third, the occurrence of hyperthyroidism and BRIC could be a coincidence without having a direct interaction. However, the latter proposition is considered less likely to be valid because no other factor seems to participate in this episode.

Hence, we might be in front of a previously proposed—but not well-documented—entity in which, in this case, hyperthyroidism inducing jaundice is favored by the underlying bile metabolism defect represented by ATP8B1 defect.[7] In our case and in the absence of other factors, hyperthyroidism seems to be the trigger. This may implicate the necessity to consider thyroid dysfunction as a probable precipitating factor in patients with BRIC presenting with a new episode.

DISCLOSURES

Author contributions: A. Halawi wrote the manuscript, reviewed the literature, and is the article guarantor. N. Ibrahim developed and analyzed the part concerning pathophysiology and interaction of liver and thyroid. A. Halawi, R. Bitar, and N. Ibrahim edited and approved the final version.

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