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SCIENTIFIC LETTER

Intrahepatic cholestasis, sometimes benign recurrent☆

Colestasis intrahepática. A veces puede ser benigna y recurrente

We present a case of atypical hepatic cholestasis in a paediatric patient. A previously healthy five-year-old male, of Romani ethnicity, who came to the emergency department due to the appearance of generalised itching and jaundice over the previous four days, together with acholia and choluria. He had had chickenpox some 10 days earlier. There were no previous similar personal or family episodes, or previous illnesses or surgical interventions.

The physical examination revealed cutaneous and conjunctival jaundice, as well as chickenpox lesions in resolution phase. The rest of the physical examination was normal.

Given the symptoms, a blood test was performed in the emergency department in which a cholestatic pattern was observed with total bilirubin of 8.63 mg/dl (normal 0.3–1.2 mg/dl), direct bilirubin of 5.61 mg/dl (normal 0–0.2 mg/dl), alkaline phosphatase 739 U/l (normal 42–362 U/l), GGT 20 U/l (normal 3–22 U/l), GOT 71 U/l (normal 0–50 U/l), GPT 101 U/l (normal 0–50 U/l) and LDH 268 U/l (normal 0–248 U/l). A haemogram, haemostasis test and a study of pancreatic and renal function were performed with normal results, as well as serology tests. The patient was referred to a paediatric gastroenterologist and a hepatobiliary ultrasound was requested in which mild diffuse hepatomegaly was found, with normal echogenicity, without focal lesions, the rest of the abdominal ultrasound examination being normal.

Treatment with ursodeoxycholic acid and colestyramine resin was prescribed. Given the biochemical pattern of cholestasis and the normality of the GGT figures, a genetic study was requested for type 1 familial cholestasis. Progressive improvement of the symptoms was observed with a complete normalisation of cholestatic parameters in less than six weeks. As a result, no more complementary studies were carried out for the time being.

The genetic study showed a pathogenic mutation in p.Thr456Met in position 1367 of exon 12 of the ATP8B1 gene, and a variant of uncertain clinical significance, probably pathological, p.Asn1029Lys in position 3087 of exon 24 of the ATP8B1 gene, both present in heterozygosity. These mutations are diagnostic of benign recurrent intrahepatic cholestasis (BRIC), which is an atypical cause of cholestasis.

It was first described in 1959 by Summerskill and Wlashe,[1] and is characterised by self-limited and recurrent episodes of severe itching and jaundice that can last from weeks to several months, sometimes triggered by viral infections. The average duration is around three months for each episode, and it can remain asymptomatic for highly variable periods, ranging from months to years.[2]

Its exact prevalence remains unknown, but the estimated incidence is approximately 1 in 50,000 to 100,000 people worldwide.[3] It is an autosomal recessive disease with incomplete penetrance, of which two forms have been described. Type 1 BRIC is secondary to a mutation in the ATP8B1 gene, located on chromosome 18 (18q21-q22), which coincides with the genetic result of the patient presented. This gene belongs to the ATP gene family (ATPase superfamily) and encodes a transporter protein (aminophospholipid transferase) that participates in the translocation of aminophospholipids at the hepatocyte level and contributes to maintaining an adequate balance of bile acids in the bile. If defective, it produces a decrease in the secretion of bile salts.

Type 2 BRIC is caused by a mutation in the ABCB11 gene, located on chromosome 2 (2q24), which belongs to the ABC (ATPBinding cassette transporters) and ATP (ATPase superfamily) gene families. This gene encodes a bile salt-exporting protein (bile salt export pump, BSEP) that mobilises bile salts from hepatocytes.

Unlike progressive familial intrahepatic cholestasis (PFIC-1), whose altered gene is the same as in benign recurrent intrahepatic cholestasis, penetrance is variable. It occurs in the first decade of life, in patients with normal psychomotor and physical development, and it is usually benign, without progression to fibrosis or liver failure, or systemic involvement. The pathophysiology of this condition is not clear, and today the pathophysiological mechanisms are unknown, although some triggers such as viral infections have been described.[4]

During the study of these patients, serological studies should be included to exclude causes of acute and chronic viral hepatitis, and medications that could cause cholestasis should be suspended. Imaging studies are also necessary to exclude obstructive biliary pathologies. In adolescents or adults, endoscopic retrograde cholangiography can be used to exclude sclerosing cholangitis or other causes of biliary tree abnormalities. Liver biopsy in the literature reviewed shows centrilobular cholestasis without liver lesions, although inflammatory infiltrates can occasionally

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be observed. In our patient, a biopsy was not performed since the abnormal test results improved in a few weeks.

Currently, there is no specific treatment to prevent or reduce the duration and severity of episodes. Treatment is based on symptom relief, until the episode resolves spontaneously. Cholestyramine and ursodeoxycholic acid have been used in the treatment of these patients for the relief of symptoms, with good response.[5] Our patient has not experienced new episodes of cholestasis in the two years following his diagnosis.

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Recurrent *Clostridium difficile* infection treated with bezlotoxumab in a liver transplant patient☆

Infección recurrente por *Clostridium difficile* tratada con bezlotoxumab en un paciente trasplantado hepático

Clostridium difficile infection (CDI) is the leading cause of hospital-acquired diarrhoea and a growing cause of community-acquired diarrhoea.[1] It has a broad clinical spectrum, and some patients with certain risk factors develop recurrent CDI (rCDI). These risk factors include: advanced age, immunosuppression, chronic kidney disease, concomitant use of antibiotics or of proton pump inhibitors (PPIs), prior episodes of CDI, and presence of hypervirulent strains such as ribotypes 027 or 244.[1,2]

CDI treatment is based on antibiotics such as vancomycin, fidaxomicin or metronidazole; the latter is now considered inferior in terms of efficacy.[1] Faecal microbiota transplantation (FMT) also plays an important role,[3,4] as it reduces recurrence by 85%–95%. Monoclonal antibodies represent a new approach to preventing recurrence. These include bezlotoxumab, which targets the micro-organism's toxin B, blocking its action and decreasing intestinal damage.[5]

We report the case of a 62-year-old man with a medical history of: hypertension; Barret's oesophagus; liver transplantation in 2005 due to liver cirrhosis (caused by hepatitis C virus and alcohol), with recurrence of hepatitis C in the transplant in 2006 (treated with direct-acting antivirals in 2015, which achieved a sustained viral response), evidence of advanced fibrosis in 2016 (12.5 kPa on elastography, METAVIR score F3), but with normal transplanted liver function parameters; osteoporosis; multifactorial chronic kidney disease (stage G3a according to the KDIGO guidelines); and two episodes of intraparenchymal cerebral haemorrhage in 2016 and 2017, with secondary vascular epilepsy, requiring prolonged hospital admission, including a stay in the intensive care unit (ICU). His regular treatment consisted of mycophenolate mofetil (500 mg/8 h), prednisone (5 mg/24 h), levetiracetam, pantoprazole and oral calcium.

In May 2017, in the last months of admission for cerebral haemorrhage, he had an initial episode of CDI that did not meet criteria to be considered severe. He was treated with a regular regimen of oral vancomycin (125 mg/6 h for 10 days), and his signs and symptoms resolved. Two weeks later, he had his first CDI recurrence, which was again treated with vancomycin, with a down-titration regimen at discharge. In October 2017, his second recurrence occurred; he was given fidaxomicin 200 mg/12 h for 10 days, responding favourably. Three months later, the third recurrence occurred and, after vancomycin treatment, underwent a first FMT. Despite this procedure, he had further recurrences in February and April 2018, and a decision was made to perform a second FMT. In the months that followed, the patient was admitted for new episodes, which were treated with vancomycin. With his eighth recurrence in March 2019, it was decided to administer bezlotoxumab during the course of treatment with vancomycin. It was administered in a single intravenous infusion for 60 min, at a dose of 10 mg/kg, with no need to make adjustments based on kidney or liver function. No short- or middle-term side effects were documented and, after 12 months, no new episodes of rCDI have occurred. It should

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