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Bardet-Biedl syndrome and hepatosplenomegaly: A case report of a rare presentation

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Abstract

Bardet-Biedl Syndrome (BBS) is a rare autosomal recessive disorder of the primary cilia with plenty of clinical manifestations secondary to the involvement of multiple organs, and difficult to diagnose. We describe an atypical case of an obese patient with metabolic syndrome and hepatosplenomegaly diagnosed with BBS after genome sequencing.

Keywords: Bardet-Biedl syndrome; Ciliopathy; Hepatosplenomegaly; Chronic liver disease.

Abbreviations: BBS: Bardet-Biedl Syndrome; BMI: Body Mass Index.

Introduction

Bardet-Biedl Syndrome (BBS) is a rare, pleiotropic and genetically heterogeneous autosomal recessive ciliopathy discovered in the 1920s and named after the researchers who first described the syndrome [1,2]. It has variable incidence estimated at 1:160,000 in Europe [3-6]. It affects both sexes equally and it is more prevalent in Arab countries having no significant epidemiological data in the South American population.

The mutations most associated with this syndrome are in BBS1 and BBS10 genes [4,5,7,8], hindering the functioning of primary cilia–sensory organelles that regulate cell signal transduction pathways. Ciliary dysfunction results in a diversity of clinical types involving multiple systems, such as the retina, nervous and genitourinary systems, liver, and heart [1,3,4,7].

The modified clinical criteria for the diagnosis of the disease proposed by Beales et al. define the clinical diagnosis by the presence of 4 major criteria or 3 major criteria associated with at least 2 minor ones. The major criteria are represented by pigmentary retinopathy, polydactyly, obesity, renal dysfunction, cognitive impairment, and hypogonadism. The minor ones are represented by hepatic and cardiac arrests, insipidus diabetes, dental anomalies, gait ataxia, brachydactyly and/or syndactyly, and developmental or speech delay [1,3,4].

Its treatment is focused on leading with clinical manifestations by a multi-professional team. The importance of early diagnosis is eminent to screen for the most prevalent complications and genetic counseling, in addition to strict control of blood pressure levels, lipid profile, and body mass [9,10].

In this article, we describe a case of BBS with an atypical clinical presentation with hepatosplenomegaly in which the diagnosis was possible only after genetic sequencing.

Case report

A 29-year-old white Brazilian female attended the medical station with intermittent abdominal pain in the right upper quadrant without precipitating factors or other associated symptoms, which would alleviate with the use of analgesics. A case of liver disease of undefined etiology ten years prior was

reported in her medical history. She also presented metabolic syndrome, obesity, dyslipidemia, systemic arterial hypertension, and type 2 mellitus diabetes. She has also had cognitive deficits with learning difficulties since childhood. There was no report of chronic liver disease or consanguinity in the family.

On physical examination, the patient was centrally obese (BMI 35.1) without any suggestions of congenital deformities in the hands or feet. An ultrasound scan of the abdomen was performed with evidence of hepatosplenomegaly and an increase in the caliber of the portal vein (17 mm), with no changes in the kidneys and urinary tract. Laboratory tests showed total cholesterol 551 mg/dL, Triglycerides 331 mg/dL, fasting blood glucose 248 mg/dL, and glycosylated hemoglobin 9.5%. Searches for autoimmune and viral depot liver diseases were negative. The investigation was carried out with a genetic panel for lysosomal diseases, presenting evidence in the SMPD1 gene of an uncertain significance variant [c.138_143 dup (p.Ala48_Leu49 dup)] in heterozygosity. Due to suspicion of Niemann Pick type B acid sphingomyelinase dosage was performed on filter paper and in leukocytes, with a result at the lower limit of normality and normal levels of chitotriosidase. Molecular analysis was then performed by complete exome sequencing, and two pathogenic variants in compound heterozygosity were identified in the BBS1 gene (Bardet-Biedl syndrome 1, OMIM* 209901), namely c.118delT CT>T and c.1169 T>G.

Discussions

BBS presents phenotypic heterogeneity, in which only 40-45% of cases have a full spectrum of clinical characteristics [2], and suspicion is necessary even in patients with incomplete clinical presentation. In these cases, molecular confirmation by genetic sequencing gains notoriety [8]. To date, mutations have been identified in 26 genes of the BBsome complex associated with BBS [11], which are present in approximately 80% of clinically diagnosed cases [3-6]. It is also understood that mutations in heterozygosity are modifiers of the phenotypic expressiveness of the disease [12]. There are no data on the cost-effectiveness of performing genetic sequencing in patients without clinical criteria for diagnosis.

In the reported case, the patient had a mutation in the BBS1 gene, with an estimated prevalence of 23.2% [3,5,6] and pertaining to a milder presence of the disease [6,13] with an incomplete phenotype for clinical diagnosis, presenting deficit cognitive impairment, central obesity, mellitus diabetes, dyslipidemia, arterial hypertension and portal hypertension with hepatosplenomegaly. The altered cognition present in 66% of cases [14] is poorly understood, but there is evidence of ciliary involvement with neurogenesis and neuronal migration [6,15]. Obesity has a variable prevalence. It affects 72-92% of individuals [2,3] being central and progressive with age. The pathogenesis may be related to defective satiety signaling in the hypothalamus with peripheral resistance to leptin like obese people in general, loss of pro-opiomelanocortin neurons, and changes in adipogenesis that have not yet been elucidated [3-5,15]. Arterial hypertension and hyperlipidemia may be secondary to obesity and occur in 30% and 60% of cases, respectively [3,6]. For most cases presented in medical literature retinitis pigmentosa, polydactyly, obesity, and developmental disorders were evident and defined by clinical criteria.

Liver involvement is rare and studies are still required in order to elucidate the pathogenic mechanism. There are records of a case of microvesicular steatohepatitis in a patient with a genetic alteration in the skipping of exons 14 and 17 in the sodium channel and Claritin ligand 1 [16]. Fatty liver disease can be secondary to obesity [11]. Other findings are mentioned, such as periportal fibrosis, small bile duct disease, perilobular fibrosis, congenital cystic dilatations of intra and extrahepatic bile ducts, portal hypertension, and biliary cirrhosis [1,17]. The patient described was diagnosed with liver disease 10 years ago and remained without etiological definition due to rarity and lack of knowledge about rare genetic syndromes, including BBS. A liver biopsy was not performed because it was denied by the patient and because it would not have elucidated the etiology of the disease in this specific case. In medical literature, patients with hepatic involvement presented portal hypertension and non-alcoholic steatohepatitis associated with classic organ involvement, thus allowing clinical suspicion [1,16,17]. The patient in the reported case meets only two major criteria: Cognitive retardation and central obesity associated with liver disease and developmental delay.

Regarding the management of the disease, medical literature recommends follow-up with a multidisciplinary team to identify and manage associated comorbidities. In the case described, screening for the involvement of other organs was performed, and no changes were identified. In addition, it was advised weight loss, and drug therapy to control dyslipidemia and glycemia, and genetic counseling was performed [9,10].

The reported case shows the need to investigate rare diseases in patients with hepatosplenomegaly without an established etiology. In this case, the patient did not meet the clinical criteria for the diagnosis of BBS. Therefore, it was only possible after genetic sequencing.

Declarations

Consent: This article complies with the Helsinki Congress and informed consent was given for publication.

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