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Bardet- Biedl Syndrome: case series and literature revision

Síndrome de Bardet-Biedl: série de caso e revisão da literatura

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Abstract

The Bardet-Biedl Syndrome is a rare autosomal recessive disorder with clinical and genetic heterogeneity. Its main characteristics are pigmentary retinopathy, obesity, polydactyly, learning disabilities, various degrees of intellectual disability, renal anomalies and hypogonadism. The objective of this study is to report two cases of the Bardet-Biedl syndrome in patients diagnosed at the Benjamin Constant Institute and to perform a literary review of the syndrome. Review of medical records and bibliographic research were made from the PubMed, SciELO, MEDLINE and LILACS databases. Currently, treatment for the Bardet-Biedl Syndrome does not exist, but early diagnosis is important to guide the child through a regular assessment of blood pressure, weight, renal imaging studies, eye exams and psychological support.

Keywords: *Pigmantary retinopathy; Genetic counseling; Low vision; Retina; Case reports*

Resumo

A Síndrome de Bardet-Biedl é uma desordem autossômica recessiva rara, com heterogeneidade clínica e genética. As principais características são retinopatia pigmentar, obesidade, polidactilia, dificuldades de aprendizado, diversos graus de deficiência intelectual, anomalias renais e hipogonadismo. O objetivo desse trabalho é relatar dois casos de síndrome de Bardet-Biedl em pacientes diagnosticados no Instituto Benjamin Constant e fazer uma revisão literária da síndrome. Revisão de prontuário e pesquisa bibliográfica nas bases de dados do PubMed, SciELO, MEDLINE e LILACS. Atualmente não há tratamento para a Síndrome de Bardet-Biedl, mas o diagnóstico precoce é importante para orientar a gestão da criança através de uma avaliação regular da pressão arterial, peso, estudos de imagiologia renais, exames oftalmológicos e apoio psicológico.

Descritores: Retinite pigmentosa; Aconselhamento genético; Baixa visão; Retina; Relatos de casos

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Introduction

Bardet-Biedl Syndrome (SBB) is a rare autosomal recessive disease. This syndrome was first described by Laurence-Moon in 1866, and Bardet and Biedl described additional cases between 1920 and 1922. The main features are pigmentary retinitis, obesity, polydactyly, learning disabilities, hypogonadism, and renal abnormalities. It is a very uncommon clinical situation affecting mainly the Arab populations in which intermarriage is common and affects both genders equally.[1,2] The etiology is uncertain, and with only a few cases are described in the literature. [2]

The objective of the present study is to report two cases of BBS in patients diagnosed at Instituto Benjamin Constant, and review the literature of the syndrome.

The report was previously submitted and approved by the Research Ethics Committee on Human Beings of Faculdade de Medicina de Valença, State of Rio de Janeiro.

Case Report

Case 1

Patient T.R.G, 16 years old, female, white, natural and from Rio de Janeiro, sought out the IBC ambulatory for ophthalmologic evaluation. She reported low visual acuity in both eyes, first observed by the pediatrician when she was 3 years old. At that time, glasses were prescribed. However, the loss of sight was progressive. The greatest visual impairment presented by the patient was mainly at night, characterizing nicotopia. In previous pathological history and in family history, there were no systemic or ocular diseases. In obstetric history, gestation was at term with natural childbirth without intercurrences. On physical examination, the patient had normal blood pressure, obesity (Figure 1) and scars for correction of hexadactyly of hands and feet (Figure 2). During the ophthalmologic exam, visual acuity with correction was lower than 20/200 in BE using the Snellen table. Goldmann Tonometry Biomicroscopy without changes. Fundoscopy of BE with pale optic disk, narrowing and decrease of the arteriolar caliber, decreased macular brightness, and important atrophy of the RPE. (Figure 3). CVM and CVC were less than 10 degrees (tubular) in BE (Figure 4). Macula OCT revealed the presence of atrophy of the sub-foveal retinal photoreceptor layer in BE. ERG showed no record of bilateral activity. The EEG showed signs of paroxysmal projective activity in posterior, bilateral, non-specific areas. The color test was also changed. The angiography of both eyes showed a pattern of hyperfluorescence in a diffuse window and focal way in the perifoveal region. Autofluorescence showed hypo-autofluorescent area in the macular region.

Case 2

Patient L.O.S, 21 years old, female, brown, native of Rio de Janeiro, sought ambulatory care at the ophthalmology department of Instituto Benjamin Constant with a complaint of progressive low visual acuity since childhood. The caregiver also refers to worsening of visual acuity at night and poor school performance. Previous history did not show systemic ocular diseases nor regular use of medication. Obstetric history with maternal diagnosis of rubella with periodic monitoring. Gestation was at term and without intercurrences. The family history showed two uncles diagnosed with open-angle glaucoma, and there was no history of consanguinity. Upon examination, the patient presented central obesity (Figure 1), hypertelorism, bilateral exotropia, mild difficulty in walking, and polydactyly in the hands and feet (Figure 5). The best corrected visual acuity was 20/100 in the right eye and 20/160 in the left eye. Echoescopy showed discrete bilateral non-alternating exotropia, narrow palpebral fissure, preserved ocular extrinsic motility, and normal direct and indirect pupillary reflexes bilaterally.

Goldmann Tonometry Biomicroscopy without changes. Funduscopy presented a large, pale and excavated optic disc with difficult evaluation, vascular tapering, yellowish-colored rounded macular lesion, and "salt and pepper" retina with areas of hypo and hyperpigmentation. (Figure 6). The computerized visual field was less than 10 degrees bilaterally, leaving only the central visual island (Figure 4). The electroretinogram showed no retinal electric response of cones or rods bilaterally. Angiofluoresceinography showed vascular thinning in the early arterial phase, diffuse hyperfluorescence pattern in window, and pseudofluorescence in the macular central area corresponding to the cicatricial atrophic area observed in the retinography. The changes were similar in both eyes. OCT showed a significant loss in the photoreceptor layer in the fovea, with disorganization of the retinal layers and the pre-retinal membrane bilaterally.

Figure 1: Patient Case 1 and Case 2 demonstrating central obesity

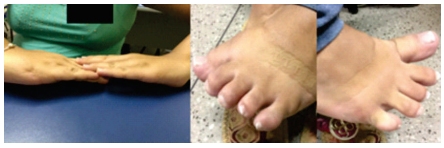

Figure 2: Patient Case 1: scars of hexadactyly correction of hands and feet

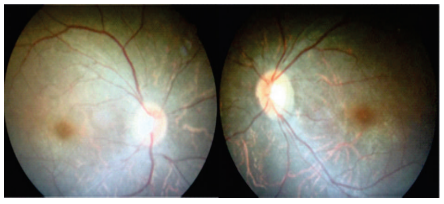

Figure 3: Patient Case 1: Color retinography presenting pale optic disk, narrowing and decrease of the arteriolar caliber, decreased macular brightness, and important atrophy of the RPE.

Discussion

BBS is considered a rare disorder: the prevalence in Tunisia was estimated at 1:156,000, and the current prevalence in European and North American populations is 1:140,000-160,000 live births. Populations with a high level of consanguinity or coming from isolated regions show a higher frequency of the syndrome.[3] Of unknown etiology, the disease presents autosomal recessive transmission, with a rate of consanguinity of

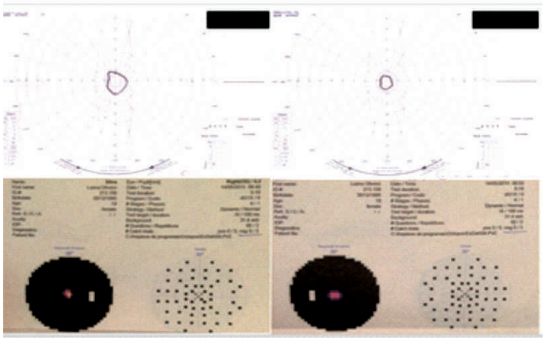

Figure 4: Patient Case 1 and 2: CVM and CVC were less than 10 degrees (tubular) in BE

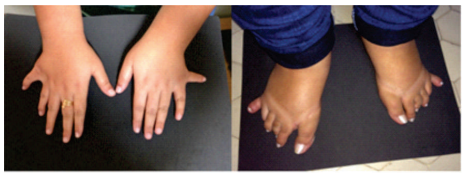

Figure 5: Patient Case 2: hexadactyly of hands and feet

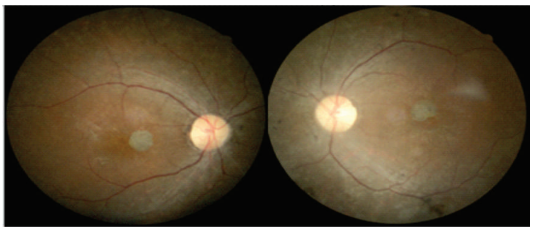

Figure 6: Patient Case 2: Color retinography presenting a large, pale and excavated optic disc with difficult evaluation, vascular tapering, yellowish-colored rounded macular lesion, and "salt and pepper" retina with areas of hypo and hyperpigmentation.

about 35%.[2] To date, 18 genes have been described (BBS1-18), corresponding to 70-80% of cases of BBS.[4,5] The BBS mutation spectrum is divergent among populations. Some patients require 3 mutations to manifest the disease.

M'hamdi et al. showed that people with BBS from the same family as the individual who had an additional heterozygous mutation (BBS6) had an earlier onset of obesity and more severe mental retardation than the sibling who carried only the homozygous p.M390R mutation (BBS1). Besides, an additional heterozygous mutation in the BBS2 gene is associated to a higher body mass index and a more severe retinal phenotype.[3]

Most of the mutations identified could not help establish a clear correlation between genotype and clinical expression of BBS. M'hamdi et al. evaluated the ocular phenotype of 37 BBS patients, and they found that patients with BBS1 mutations had a milder phenotype than patients with mutations in other BBS genes. The extensive clinical and genetic heterogeneity of BBS raises difficulties for molecular diagnosis and genetic counseling. In the last decade, many molecular strategies have been proposed to increase the frequency of mutation detection. Recently, the implementation of state-of-the-art sequencing has accelerated the molecular analysis of patients with BBS.[3]

Stigglebout W et al. developed the criteria for the diagnosis of BBS: the presence of 4 main characteristics, or the combination of 3 main characteristics and 2 secondary characteristics. The main features are: retinal dystrophy, polydactyly, obesity, learning disabilities, hypogonadism, and renal abnormalities. Among the secondary characteristics are: speech disorder, strabismus, cataract, astigmatism, syndactyly, brachydactyly, developmental delay, polyuria, polydipsia, small root of teeth, hypodontia, high palate, left ventricular hypotrophy, diabetes mellitus, congenital heart disease, hepatic fibrosis, ataxia, poor coordination, and imbalance.[1,2,4]

The patients had four main characteristics (retinal dystrophy, polydactyly, obesity, learning difficulties), and some secondary characteristics (speech disorder, strabismus, astigmatism, brachydactyly, developmental delay), confirming the diagnosis of the syndrome.

The most characteristic fundoscopic exam of BBS is atypical pigmentary retinal dystrophy with early macular involvement. The function of cones and rods is affected at BBS.[2,5] The patients had an eye fundus examination compatible with pigmentary retinitis. However, the patients did not present the bone spicules in the periphery, but an atypical pigmentary retinal dystrophy typical of BBS. Unlike typical RP, BBS retinopathy affects VA earlier. Visual acuity, dark adaptation, and peripheral CVC are affected.

Although there is currently no treatment for BBS, early diagnosis is important for possible genetic counseling and during prenatal care, to guide the child's follow-up through a regular assessment of weight, blood pressure, ophthalmic exams, imaging studies, and psychological support. It is recommended that all patients diagnosed with BBS syndrome are followed by a multidisciplinary team. The ophthalmologist plays an important role, and the patient should have regular appointments. To date, no treatment has proven effective for RP, but these patients may benefit from the use of low-vision aids, improving patients' performance in their daily activities.

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