

BARDET-BIEDL SYNDROME – CASE PRESENTATION

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ABSTRACT

Bardet-Biedl syndrome (autosomal-recessive inheritance) is characterized by obesity, retinal dystrophy, polydactyly and mental retardation. The authors emphasize the necessary steps in order to establish the diagnosis for an infant with overweight, polydactyly and hypogenitalism.

Keywords: Bardet-Biedl syndrome, obesity (overweight), polydactyly

INTRODUCTION

Bardet-Biedl syndrome (BBS) is a condition consisting of multiple anomalies: vision loss, early onset obesity, polydactyly and mental retardation.

At the end of XIXth century, John Laurence and Robert Moon described four patients with retinitis pigmentosa, mental retardation, spastic paraparesis, short stature and hypogenitalism. In 1920 George Bardet, based on analysis on hypothalamic obesity, described a patients group with obesity, retinitis pigmentosa and hexadactyly. Then, in 1922, Artur Biedl published a study about siblings with polydactyly and intellectual impairment. In 1925 it was decided that the disorders described by all four physicians were the same and the disease was named Laurence-Moon-Bardet-Biedl syndrome. Recently, this syndrome was split into Laurence-Moon syndrome characterized by spastic paraparesis and mental retardation and Biedl-Bardet syndrome (BBS) that implies obesity, polydactyly and learning difficulties.

Etiology

BBS belongs to ciliopathies, like other disorders: primary ciliary dyskinesia/ Kartagener syndrome, hy-

drocephalus, polycystic kidney disease, Meckel-Gruber syndrome, Joubert syndrome (1). The genetic background of SBB is heterogeneous, including 15 genes. Even though SBB is autosomal-recessive inherited, in some cases two mutations in one BBS gene and a third mutation in secondary locus are necessary for BBS phenotype (triallelic inheritance) (2). The 4 most commonly involved genes are BBS1, BBS2, BBS10 and BBS12, their screening identifying almost 62% of BBS patients (3). The *BBS12* gene anomalies (vertebrate specific gene) is responsible for 6% of SBB patients. *BBS12*, *BBS6* and *BBS10* genes are type II chaperonins and are specifically involved in ciliary functions (4).

There are differing disease phenotypes in accordance with involved BBS gene (2):

- BBS patients with *BBS2/BBS4* mutations are significantly shorter than their parents;
- BBS3 patients have polydactyly (lower limbs), obesity and low IQ;
- BBS5 subjects have severe visual impairment and brachydactyly/syndactyly, but no polydactyly;
- the *BBS6* mutation is also responsible for McKusick-Kaufman syndrome, a disorder with surprising phenotypic overlap (5).

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Pathophysiology

There is a complex interaction between genetic factors and ciliary dysfunction. In context of severe impairment of tubule cilia function, renal failure will be a leading cause of mortality in BBS (6).

Epidemiology

The disease prevalence in Europe and North America is around 1 in 150,000 newborns. A high incidence is reported in Bedouins and Arab population of Kuwait (1:13,500). Ratio of male: female is approximately 1.3:1.

The BBS patients present following features, (7):

- obesity (83% of patients);
- mental retardation (IQ of 79 or below in 77% of patients);
- limbs anomalies: postaxial polydactyly (58%), syndactyly, brachydactyly (50%);
- ocular abnormalities: retinal dystrophy (100%), myopia (75%), astigmatism (63%), nystagmus (52%), glaucoma (22%), posterior capsular cataract (44%), retinitis pigmentosa (8%);
- cardiac abnormalities: hypertrophy of inter-ventricular septum/left ventricle and dilated cardiomyopathy;
- urinary tract anomalies: abnormal calyces (95%), renal cysts (62%), focal scarring (24%), ectopic urethra;
- genital anomalies: hypogenitalism in males (small penis/testes), uterus duplex, uterus hypoplasia, septate vagina, vaginal atresia;
- other anomalies: hepatic fibrosis, diabetes mellitus, diabetes insipidus, clinodactyly of the 5th finger, hearing loss, hippocampal dysgenesis.

In evolution, patients can develop neuropsychiatric symptoms (obsessive-compulsive disorder, attention difficulties), schizophrenia, ataxia, renal tubular acidosis, renal failure, hypertension, bronchial asthma (in 25% of cases). Visual acuity deteriorates with age.

Investigations

The probable diagnosis is established based on clinical features, but its confirmation requires genetic testing to differentiate BBS from other rare genetic disorders.

The evaluation of renal and cardiac functions (blood tests and imagistics) is recommended for prognosis assessment.

Treatment

There is no specific treatment for BBS.

The prognosis is poor when renal failure occurs.

Prophylactic measures. The genetic counseling and preconception genotyping of genitors are useful.

CASE PRESENTATION

C.V.N, 5 month-old male infant, was admitted in pediatric department for further evaluation and treatment in context of breathing difficulties, coughing and nasal obstruction.

Family history: healthy and non-consanguineous parents; mother VI Gesta V Para (a miscarriage); the index case is the 5th child in the family; the two brothers and two sisters of infant are healthy; one sister (15 years old) presented during childhood primary teeth anomalies (she changed four times the maxillary central incisors). Obstetric history: birth at 9 months gestational age (cephalic presentation); birth weight 3,800 g; APGAR score = 10/1 minut.

Patient history: three hospitalisations justified by acute bronchiolitis.

The clinical exam: abundant adipose tissue, weight = 10.8 kg (>95th percentile), head circumference = 41 cm, facial dysmorphism (up-slanted palpebral fissures, low-inserted hair anteriorly), skin pallor, bilateral accessory nipples (polithelia), skin dryness (xerodermia), seboreic dermatitis of scalp, palmar simian crease; short neck, rickets signs, digits anomalies (brachydactyly, postaxial polydactyly – bilateral foot, partial syndactyly affecting toes 5 and 6 on left foot); hypotonia; arm/forearm ratio <1; pubis to vertex / pubis to floor ratio >1; nasal obstruction, rhinorrhea, 46 breaths/minut, dry coughing, wheezing, dyspnoea, prolonged expiration, sibilant crackles, a grade 1/6 systolic murmur, 120 beats/minut; congestion of pharynx, normal macroscopic appearance of the urine, hypogenitalism (small penis, small testicles); no meningitis signs, delayed motor skills (according to age of two months).

Investigations

Blood tests: leukocytes 12.190/mm³ (lymphocytes 67%, neutrophils 17%, monocytes 13%), haemoglobin = 10,6 g/dl; platelets = 395.000/mm³; C reactive protein = 1 mg/L (normal < 10), hepatic and renal markers within normal range; normal values for iron, glucose, cholesterol and triglycerides; alpha 1-antitripsine in reference range.

Urinalysis was normal.

Iontophoresis test: normal result.

Imagistic assessment: abdominal ultrasound exam without pathological features; the echocardiogram revealed moderate hypertrophy of interventricular septum and left ventricle, hypertrophic cardiomyopathy.

Ocular fundus exam: no retinal dystrophy.

Differential diagnosis included:

– Bardet-Biedl syndrome can be considered in this case due to overweight, polydactyly and hypogenitalism;

– Laurence-Moon syndrome (LMS); LMS patients are affected by spastic paraparesis, but no polydactyly, so this disease is considered less probable;

– Cohen syndrome is characterized by intellectual disability, microcephaly, hypotonia, joint hypermobility, myopia, retinal dystrophy, obesity around the torso with slender arms and legs (onset during adolescence) and face dysmorphism (bulbous nasal tip, prominent maxillary central incisors). In context of normal head circumference/absence of dysmorphism in conjunction with early onset obesity, Cohen syndrome was ruled out;

– Alstrom syndrome is a genetic autosomal-recessive inherited disease; the illness starts in infancy and consists in short stature, retinal dystrophy with progressive loss of vision, obesity, dilated cardiomyopathy, type 2 diabetes mellitus and deafness (8); this disorder can't be excluded;

– McKusick-Kaufman syndrome (MKKS) is a genetic condition involving polydactyly, congenital heart disease and genital abnormalities (9,10); the clinical features of MKKS overlap with those of BBS, except vision loss, obesity and renal failure; MKKS is less probable (early onset obesity);

– Carpenter syndrome is a condition characterized by craniosynostosis, digits anomalies (polydactyly, brachydactyly, cutaneous syndactyly), intellectual disability, early onset obesity and facial dysmorphism (down-slanting palpebral fissures, low set ears) (11); due to craniosynostosis absence, this disorder was ruled out;

– Simpson-Golabi-Behmel syndrome (SGBS) is consistent with macrosomia, coarse face (hypertelorism, macrostomia, broad nose), one or more rudimentary nipples (polythelia), postaxial polydactyly, hepatosplenomegaly, cardiac malformation and kidney abnormalities, (12); in context of non-suggestive face for SGBS correlated with absence of hepatosplenomegaly, this disorder was excluded;

– Prader-Willi syndrome is a condition characterized by hypotonia, late onset obesity (during

childhood), type 2 diabetes mellitus, mental retardation, short hands and feet, underdeveloped genitals, (13); this condition is considered less probable because of atypical (during infancy) onset of overweight.

Positive diagnosis

The patient phenotype (overweight, postaxial polydactyly, partial syndactyly, genital anomalies) correlated with cardiac malformation (hypertrophy of interventricular septum and left ventricle) indicated the possibility of BBS, justifying genetic assessment (Nijmegen, The Netherlands) including the screening of all known genes associated with BBS. The genetic evaluation was performed not only for infant, but also for genitors and consisted in "next generation DNA sequencing". This revealed a homozygous nonsense mutation in BBS12 (c.1063C > T, p.Arg.355). This mutation was first reported to be associated with BBS by Stoetzel et al. in 2007 (4). Both parents are heterozygous carriers for the variant.

Based on genetic test, the authors considered BBS diagnosis in an infant with acute bronchiolitis and recurrent wheezing.

Treatment

The bronchiolitis therapy included inhaled beta2 agonists, intravenous corticosteroids and D vitamin orally (good evolution). For BBS, there is no specific therapy.

In evolution, it's recommended to follow-up the case regarding few aspects:

- supervision of hypocaloric diet with growth chart monitoring;
- periodic clinical evaluation;
- therapeutic evaluation: initiation of leukotriene receptor antagonists in context of persistent wheezing;
- periodic blood investigations including: glucose, creatinine, blood urea nitrogen, triglycerides, cholesterol and endocrine assessment (thyroid function tests, testosterone level);
- imagistic assessment (abdominal ultrasound exam, echocardiogram);
- surgical excision of accessory digits may be necessary.

CONCLUSIONS

1. The authors present a male infant with overweight, postaxial polydactyly and hypogenitalism that was genetically confirmed as Bardet-Biedl syndrome.

2. The genetic evaluation of probant's siblings is useful, considering the wide spectrum of phenotype, from mild type to severe disease.
3. The genetic counseling is worthwhile in order to diminish the genetic condition in the family.
4. In front of a patient featuring obesity, postaxial polydactyly and mental disabilities, it's important also to consider the possibility of Bardet-Biedl syndrome.

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