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Clinical Aspects of a Rare Disease: Bardet Biedl Syndrome

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Abstract

Bardet Biedl syndrome (BBS) is a rare primary ciliopathy with a complex and extremely variable clinical presentation. The core features of the disease are rod-cone dystrophy, postaxial polydactyly, central obesity, urogenital anomalies, learning difficulties and kidney disease, however the impairment of any organ may complicate the clinical picture. Here we report on clinical findings of 25 patients diagnosed with BBS. Our study is the first on a cohort of Romanian BBS patients, aiming to emphasize the complexity of the disease that may have a devastating impact on patients and their families. Thus, an early clinical diagnosis is crucial for anticipation of other system and organ involvement. Periodic follow up, by a multidisciplinary team, may prevent several severe complications, which could accelerate or aggravate the most deleterious aspects of the disease: loss of vision or renal impairment.

Keywords: Bardet Biedl syndrome, ciliopathies, multiorgan involvement, pleiotropy, oligogenic, inheritance.

Rezumat

Sindromul Bardet Biedl (SBB) este o ciliopatie primară rară, cu o prezentare clinică complexă și extrem de variabilă. Trăsăturile clinice principale ale bolii constau în: distrofie retiniană, polidactilie postaxială, obezitate de tip central, anomalii urogenitale, dificultăți cognitive și boală renală, însă, tabloul clinic poate fi complicat de afectarea oricărui organ. În acest studiu, descriem simptomatologia unui lot de 25 de pacienți diagnosticați cu SBB. Studiul nostru este primul care analizează o cohortă de pacienți români cu SBB, având ca scop sublinierea complexității bolii și a impactului devastator pe care aceasta îl poate avea asupra pacienților și asupra familiilor acestora. Prin urmare, un diagnostic clinic precoce este crucial în anticiparea implicării și altor organe sau sisteme. Monitorizarea periodică de către o echipă multidisciplinară poate preveni apariția unor complicații severe, care ar putea accelera sau agrava cele mai invalidante aspecte ale bolii: pierderea vederii și afectarea renală.

Cuvinte cheie: sindromul Bardet Biedl, ciliopatii, afectare multiorganică, pleiotropie, variabilitate, transmitere oligogenică.

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INTRODUCTION

Bardet Biedl syndrome (BBS – Mendelian Inheritance in Man, MIM: 209900) is a rare pleiotropic genetic disorder, with variable clinical features among individuals and even within families[1]. The prevalence of the disease is 1:160.000 in European population, that could significantly increase in isolated and consanguineous communities[2]. It belongs to an extensive category of disorders, named ciliopathies that arise as a result of primary cilia defects, either structural or functional[3]. The disease is characterized by a core of features consisting in: rod-cone dystrophy, postaxial polydactyly, central obesity, urogenital anomalies, learning difficulties and kidney disease. Additional clinical findings: neurodevelopmental and behavioral abnormalities, liver involvement, endocrine and metabolic abnormalities, oral-dental anomalies, craniofacial dysmorphic features, cardiovascular impairment, and hearing loss, complete the clinical pictures[4]. Considering the remarkable heterogeneity, the clinical diagnosis is not easy to establish, however, a clinical diagnostic criteria have been proposed by the presence of four major findings or by combination of tree major features with two minor symptoms (Table 1)[1]. Nevertheless, a recent metanalysis suggested that not all patients, molecularly diagnosed with BBS, fulfilled the consensus criteria for clinical diagnosis[5].

Several signs could be observed antenatally, i.e., polydactyly, enlarged kidneys or abdominal distension due to the genitourinary malformations, that may raise the suspicion of the diagnosis. These findings, although not specific for BBS, combined with molecular tests during the pregnancy could establish the diagnosis[6,7]. Yet, in the absence of a family history, the diagnosis is rarely done before birth. Nevertheless, these children could be diagnosed earlier than those with no renal or genitourinary involvement. Commonly, the age of clinical diagnosis varies between five and ten years, once the retinal degeneration become apparent[8]. Night blindness is the first symptom of this atypical retinal dystrophy that has an early macular involvement. Due to the progressive loss of the rods and cone cells, patients develop decreased peripheral vision, loss of visual acuity and color distinguish, becoming legally blind at the mean age of 15.5[9]. Other ocular involvements include strabismus, astigmatism, cataracts, and optic atrophy[1]. In the majority of patients, the birth weight is normal or toward to the upper limit. The gain in weight starts in the first year of life and obesity becomes obvious at the age of two-three years[2]. About 16%-25% of patients develop a morbid obesity (body mass index – BMI >40kg/m^2)[1]. Comorbidities, such as hypertension, hypertriglyceridemia, hypercholesterolemia or diabetes mellitus, are frequently seen in obese BBS patients[10,11]. Polydactyly, usually postaxial, could be easily observed antenatally or since birth and may interest all limbs or only the hands or only the feet. Often, it is associated with brachydactyly and, in some patients, with partial two-three fingers syndactyly[1]. Kidney disease is the main cause of morbidity amongst BBS patients, leading to renal failure. Most children develop the renal symptoms before the age of ten[12]. The main feature consists in cystic tubular disease, but a wide variety of other renal abnormalities has been reported: ectopic, duplex or horseshoe kidney, atrophic kidneys with normal or irregular shape, calyceal distortion, hydronephrosis, renal agenesis[1, 13, 14]. Dysplastic renal disease or glomerulosclerosis are additional signs. Urinary concentration defects are common; proteinuria and albuminuria have been also noted[12]. Urogenital anomalies are penetrant in BBS patients. In male, small penile size and hypogonadism have been seen in almost all patients, while in female hypoplastic labia minora, vaginal atresia, septate or imperforate vagina, are the most common findings[14,15]. Cognitive difficulties are often seen in BBS individuals and, generally, are mild to moderate. The majority of cases experience a remarkable weaker performance in perceptual reasoning, verbal fluency, attentional capacity and functional independence[16]. Developmental delay, either global or affecting only distinct areas, has been reported. Most children are delayed in attending milestones, while speech deficit, i.e., high-pitched voice, misarticulation, consonant substitutions and omission of the last syllables, are common in BBS patients[17]. Various behavioral abnormalities reported in BBS individuals include: emotional lability, disinhibition, depression, panic attacks, obsessive-compulsive attitude, lack of social interaction and autistic spectrum disorders[18]. Several dysmorphic features are specific, but could be inconstant in BBS patients: „moon" face, narrow forehead, down slanting palpebral fissures, deep set eyes, hypertelorism, depressed nasal bridge, anteverted nares, and retrognathia. Less frequent noted, cardiovascular involvement such as atrioventricular septal defects, valvular stenosis, bilateral persistent superior or interrupted inferior vena cava and cardiomyopathy may complicated the clinical pictures and,

Table 1. *Consensus criteria for clinical diagnosis of BBS*

Major (primary) featureas	***Minor (secundary) features***	***Diagnostic***
	Developmental delay	
	Speech delay	
Retinian dystrophy	Ataxia/ poor coordonation	
Polydactyly	Behavioral abnormalities	***4***
Obesity	Oral/dental abnormalities	***Primary features***
Genitourinary anomalies	Craniofacial dysmorphism	
Renal anomalies	Metabolic syndrome	***or***
Learning dificulties	Endocrine abnormalities	
	Brachydactyly/syndactyly	***3 primary and 2 secondary features***
	Cardiovascular abnormalities	
	Liver disease	
	Gastrointestinal diseases	

in some cases, could be diagnosed antenatally or early in infancy. Occasional, Hirschsprung disease or other gastrointestinal involvement, hearing loss, skin abnormalities and laterality defects have been reported[4].

26 genes have been linked with BBS phenotype, so far, and their encoded proteins have been associated with primary cilium biogenesis and function[19]. Although BBS is classical inherited in an autosomal recessive manner, oligogenic inheritance has been assigned to the majority of BBS genes. The variable expressivity of the phenotype is related to a complex genetic mechanism that characterized the disease including: second site modifier, epistatic interaction or epigenetic changes[8, 20, 21].

AIM

Here we are analyzing the clinical aspects of 25 patients diagnosed with BBS. This research is the first study on a cohort of Romanian BBS patients. The main goal is to raise the awareness of medical community regarding the complexity of this disease and to highlight the importance of an early diagnosis that may be essential for the management of the patients.

MATERIAL AND METHODS

Our research study focused on clinical aspects of patients with BBS. The study was approved by Institutional Review Board of University of Medicine and Pharmacy "Carol Davila" Bucharest, with respect of Declaration of Helsinki. Written informed consent was obtained from the patients and from their legal guardian.

Diagnosis was made according with consensus criteria established by Beales et al. by the presence of four major features or three major features and two secondary features (Table 1) [1]. The patients were fully evaluated by multidisciplinary team, including a pediatrician, child psychiatrist, child neurologist, psychologist, ophthalmologist, endocrinologist, nephrologist and clinical geneticist. Clinical examination, medical history, dysmorphology examination, physical measurements, imagistic studies and blood tests screening, were performed.

RESULTS AND DISCUSSIONS:

25 patients, 16 females and 9 males were recruited, of which two are siblings. The age at the time of enrolment varied between 2 months and 43 years. 76% of patients were under 18 years old. Most patients had the age between 1 and 10 years, 76% respectively. 8% were under 1 year old, 8% were between 30 and 40 years old and 4% were over 40 years.

The age of the clinical diagnosis was, in the majority of cases, in the first year of life, which is lower comparing with other studies. Previous research indicated that the age at diagnosis varied between 5 and 10 years, age at which rod cone dystrophy became symptomatic[8]. However, suggestion that BBS could be suspicioned even antenatally or immediately after birth were based on the presence of polydactyly, renal or genitourinary malformation[6]. According with these reports, the suspicion of BBS diagnosis was raised antenatally in one of our cases, while in two cases the diagnosis was made shortly after birth. Other two cases were diagnosed later at 11, and 12 years, respectively.

Major clinical findings were distributed in our cohort as follows (Figure 1):

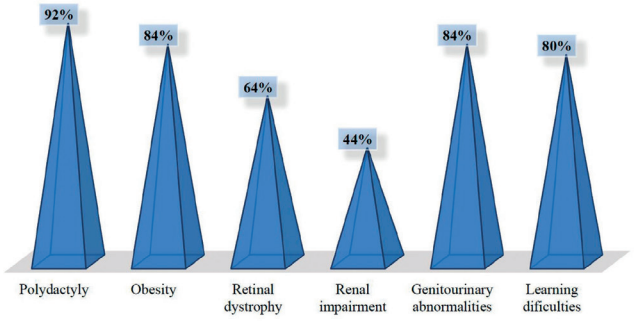

Figure 1. Distribution of primary clinical findings in our cohort

Polydactyly were observed in 92% of the cases. The accessory digits were present in all four limbs in 52% of patients, only on the feet in 16% or only on the hands in 4%. In 4% the polydactyly was present in both hands and one foot, in 4%, extra digits were present in one hand and both feet, while 12% of cases exhibited polydactyly only in the left limbs. The higher percentage of polydactyly in our cases, comparing with previous reports (63-81%)[2,4,8] may be explained by a limited number of patients enrolled in the study, however could also suggest a lower rate of diagnosis in BBS patients without polydactyly.

Obesity was recorded in 84% of our patients, in accordance with literature (72-92%)[1,2,8]. Typically, the birth weight is normal and the weight gain commences in the first year of life. In our cohort, the birth weight was towards to the lower percentiles in 40% of the cases, however, within the normal range. Of these, 12% of children was on percentile 1. 28% of children had a normal birth weight. 12% of children had birth weight towards to the upper percentile, while 16% had birth weight above the upper percentile. Retinal dystrophy was present in a lower percentage in our cohort, 64%, comparing with previous reports (93-94%)[1, 2, 4]. This inconsistency may be due to the young age of some patients in our study, or due to the small number of cases enrolled. Remarkable, the visual deficit was observed in the first year of life in two patients and in the first three years of age in other two cases, earlier than previous reports. Genitourinary anomalies were noted in 84% of our patients, consistent with literature (59-98%)[2,4,8]. All males had small penile size, while 31% of the females had vaginal atresia and other 37% had hypoplastic genitalia.

Renal involvement was identified in 44% of our patients in accordance with previous reports (25-53%)[1,8]. The most frequent anomaly was hydronephrosis seen in 20% of patients, followed by polycystic kidney in 16%. Other structural anomalies, i.e., hypoplastic or atrophic kidney, were detected in 12% of cases. Renal dysfunction affected 28% of cases of which 12% it has progressed to end stage renal disease, and 4% undergone renal transplantation.

Learning difficulties were present in a higher percentage in our patients 80% comparing with previous studies (61-66%)[2,4], which may be due to the small number of patients enrolled, or due to different scale used in evaluation of the patients in our cohort.

Main secondary features were present in our patients as following (Figure 2): psychomotor delay was

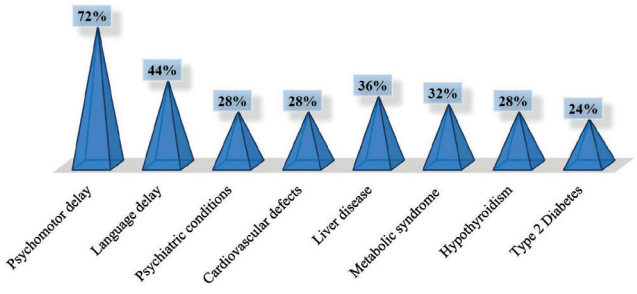

Figure 2. Distribution of main secondary findings in our cohort

noted in 72% of our patients, language delay was observed in 64%, while psychiatric conditions affected 28% of patients. Cardiovascular defects were present in 28% of cases, hepatic involvement in 36%, metabolic syndrome in 32%, while hypothyroidism and type 2 diabetes were remarked in 28%, respectively 24% of cases. Some of these features are consistent with previous reports, including psychomotor delay (50-81%)[1,4], language delay (54-81%)[1,2], cardiovascular involvement (7-29%)[2,4], type 2 diabetes (6-48%)[2] and hepatic involvement (30%)[4]. Slightly below average reported in previous studies were psychiatric abnormalities (33-35%)[1,4] and below average was metabolic syndrome (54%)[4], while hypothyroidism was much frequent in our patients comparing with literature (20%)[4]. These findings could be assigned to the small number of patients enrolled in the research; however, it may also suggest a hallmark of our population modulated by diet or by environmental influence.

All of our patients had a multisystemic involvement. Many of they were severely affected. Our study confirms the broad clinical presentation of BBS shown in previous reports. Recognition of signs and symptoms of the disease is decisive for an early diagnosis. Thus, the presence of polydactyly in a new-born or even in a fetus, especially in association with other suggestive features, should raise the suspicion of BBS. Enrollment of the patients as soon as possible in a strict monitoring program, accordingly with international guidelines, may prevent some severe complications, which could accelerate or aggravate the most deleterious aspects of the disease such as loss of vision or renal impairment.

CONCLUSION

This is the first analysis of the clinical picture of BBS on a cohort of Romanian patients.

BBS is a complex disease which affect the majority of systems and organs (brain, eye, heart, liver, kidney, limbs, genitalia) therefore it has a devastating impact on patients and their families. An early clinical diagnosis of these patients is crucial for anticipation of other phenotypic involvement. Periodic follow up, by a multidisciplinary team, may help in limiting the comorbidities and in improving the life quality of BBS patients.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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