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Bardet-Biedl Syndrome: Clinical, Endocrinological and Imaging Evaluation of Three Unrelated Bedouin Children

Key Words

Bardet-Biedl syndrome
Hormonal profile
Phenotype variability
Genetic heterogeneity

Abstract

Objective and Importance: Bardet-Biedl syndrome (BBS) is a heterogeneous disorder; clinical dissimilarities do exist among patients. Cases of BBS have been reported with hypertension, diabetes mellitus and renal disease, while others were reported with hepatic disease. Here, we are reporting 3 newly diagnosed unrelated Bedouin children, evaluated for the presence of an endocrine disorder. **Clinical Presentation:** Our patients were 2 males and 1 female. These patients are obese with a voracious appetite, postaxial polydactyly and mentally retarded. Pigmentary retinopathy was found in the older children and hypogenitalism is apparent in the older male child who is also hypertensive. The clinical, endocrinological and imaging evaluation data are compared with previously published cases. Also, phenotypic variability and genetic heterogeneity of BBS pleiotropic gene are briefly discussed. **Conclusion:** The results of hormonal studies in our cases showed no endocrinological dysfunction, except for the presence of hypogonadism. Although no specific treatment is available, an early evaluation of BBS cases can be the first step in initiating symptomatic management and preventive measures for the patient and the family.

Introduction

In 1970, Amman [1] considered the sibs reported by Laurence and Moon [2] with mental retardation, retinopathy, hypogona-

dism and spastic paraplegia but without marked obesity and polydactyly to represent a distinct entity, the Laurence-Moon syndrome (LMS). This is different from the syndrome described by Bardet [3] and Biedl [4], where

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marked obesity and postaxial polydactyly are additional features but without paraplegia for which the Bardet-Biedl syndrome (BBS) is preferred. Recently, the nosologic splitting of the Laurence-Moon-Bardet-Biedl syndrome (LMBBS) into two different but interrelated autosomal recessive disorders (BBS and LMS) has been widely accepted (MIM 209900 and 245800 McKusick) [5].

Herein, we report the results of clinical, endocrinological and imaging evaluation of 3 unrelated Bedouin children with BBS, and the phenotypic variability of its pleiotropic gene is briefly discussed.

Case Reports

Patient 1

Our first patient is a 13-year-old boy (fig. 1) who was born to healthy consanguineous Bedouin parents with 10 phenotypically normal sibs. Since late infancy, his mother noticed that his growth was considerably different than in his peers, with above average weight, voracious appetite and symptoms of night blindness. On examination he was apathetic with postaxial polydactyly of the right hand and foot, obese (weight 103.5 kg, >95 centile), blind with fine nystagmus, equally dilated pupils and sluggish in its response to light. Ophthalmological examination showed pale optic discs with sharp edges, attenuated retinal vessels, mild retinal edema and pigmentary retinopathy. He was on Inderal tablets (10 mg, 4 times daily), hypertensive (BP = 190/120), and had a normal cardiovascular system. He showed no symptoms of hypertonia or weakness, though his deep tendon reflexes were brisk with equivocal plantar reflexes. He had hypogenitalism with micropenis (the stretched penis length is 2.6 cm), hypoplastic scrotum and bilateral cryptorchidism with normal pubic hair and scanty axillary hair. Hormonal profile study showed normal follicle stimulating hormone (FSH), luteinizing hormone (LH), fasting blood glucose, plasma insulin, thyroid function, and cortisol level with mild lower level of testosterone. Routine laboratory investigations showed normal values for complete blood count (CBC), serum electrolytes, blood urea nitrogen (BUN), serum creatinine, serum cholesterol, serum uric acid and fasting serum triglycerides. Head CT scan showed mild cortical atrophy with normal EEG. Peripheral blood culture showed 46,XY karyotype.

Fig. 1. Patient 1 showing obesity and postaxial polydactyly of the right hand and right foot.

Patient 2

Our second patient is a 7-year-old girl (fig. 2), who was born to healthy consanguineous Bedouin parents with 4 phenotypically normal sibs. Her mother noted her delayed milestones and voracious appetite.

Our examination revealed that she was mentally retarded, obese (51.5 kg, > 97 centile) with coarse features, facial hirsutism, sparse axillary and pubic hair, striae on her abdomen, buttocks and upper thighs, and postaxial polydactyly in both feet. Her vision was moderately impaired with equal regular pupils, and responding normally to light. Fundoscopy revealed pale optic discs, attenuated retinal vessels and pigmentary retinopathy. External genitalia were of normal female type. Moderate gynecomastia was present without galactorrhea. Her hormonal profile showed low FSH, elevated LH, low normal estrogen and normal fasting blood glucose and insulin levels. Routine laboratory investigations showed normal results including CBC,

Fig. 2. Patient 2 showing coarse features, obesity and postaxial polydactyly of both feet.

serum electrolytes, BUN, serum creatinine, alkaline phosphatase, calcium, phosphorus, fasting serum cholesterol and triglycerides. Abdominal ultrasonography and intravenous pyelography showed no renal anomalies or pyelonephritis. Pelvic sonography also showed no abnormality. Slipped capital epiphysis of left femur was found on skeletal survey.

Head CT scan showed mild cortical atrophy, more in the frontal region with mild dilatation of the third and lateral ventricles. EEG was normal and peripheral blood culture showed 46,XX karyotype.

Patient 3

Our third patient is a 1-year 9-month-old boy who was born to healthy consanguineous Bedouin parents with 1 phenotypically normal brother. Our patient presented with micropenis (the stretched penis length is 1.3 cm), delayed speech, increased appetite and was

polydactyly. On examination, he was grossly obese (weight 16 kg, >97 centile), height 82 cm (>10 centile), head circumference 48 cm (25 centile), with hypertelorism and a fish-like mouth, postaxial polydactyly of the left hand and both feet, splenomegaly (enlarged 3.5 cm below costal margin), and mild developmental delay. An ophthalmological examination revealed normal vision, pupils and fundoscopic examination. Hormonal profile showed normal growth hormone, FSH, LH, thyroid stimulating hormone (TSH), free thyroxine (FT₄), serum cortisol and fasting insulin level with mild elevation of fasting blood glucose. Routine laboratory tests were normal. Abdominal ultrasound showed fetal lobulation of his right kidney. Head CT scan showed mild dilation of the ventricular system. EEG was normal. Peripheral blood culture showed 46,XY karyotype.

The biological and phenotype variables of the 3 Bedouin children with BBS are summarized in table 1, and their hormonal profile and cytogenetic findings are summarized in table 2.

Discussion

Since the first report of BBS (formerly LMBBS) in an Arab family [6], many literature reports of this syndrome among Arab populations were published [7–14]. In Kuwait, 13 families with 20 BBS patients (13 males and 7 females) were reported in a 7-year study (1979–1986), and another 16 cases of BBS in 11 new families were reported during a second community genetic program (May 1989) [11, 12]. This raises the previously estimated overall prevalence among the mixed Arab population in Kuwait from 1 in 65,000 to 1 in 36,000. The 24 patients reported from 17 families had Bedouin ancestors showing high minimum prevalence of BBS among Bedouins (1 in 13,500). This is about 3 times higher than the figures from the mixed Arab population of Kuwait and at least 10 times higher than that from Switzerland [15, 16]. Thirteen of the Bedouin patients were born between 1979 and 1989 in the Jahra province (>85% Bedouins) out of approximately 95,000 live births with an incidence of 1 in

Table 1. Biological and phenotypic variables of the 3 Bedouin children with BBS

	Patient 1	Patient 2	Patient 3
Age, years	13	7	1 ⁹ / ₁₂
Sex, M/F	M	F	M
Weight, kg	103	51.5	16
Height, cm	152	126	82
Truncal obesity (>95 cm)	+	+	+
Postaxial polydactyly	+	+	+
Developmental delay and mental retardation	+	+	+
Impaired visual acuity	+	+	–
Night blindness	+	+	–
Retinal pigmentation	+	+	–
Hypogenitalism	+		+
Lobulated kidney	–	–	+
Hypertension	+	–	–
Head CT scan			
Cortical atrophy	+	+	–
Dilated ventricles	–	+	+

Table 2. Hormonal profile and cytogenetic findings of the 3 BBS children

	Patient 1	Patient 2	Patient 3
Growth hormone (0–18 mIU/l)	4.9	6.8	6.3
FSH (0.5–3.3 IU/l)	1.4	<1.0	0.79
LH (0.3–1.0 IU/l)	0.74	2.1	0.45
Estrogen (22–139 pmol/l)	–	27	–
Testosterone (5.2–22.9 nmol/l)	5	–	14
Cortisol (200–650 pmol/l)	289	351	276
TSH (0.23–4.0 mIU/l)	2.5	3.9	1.12
FT ₄ (11.8–24.6 pmol/l)	19.7	10.6	11.44
Fasting blood sugar (3.9–6.1)	5.2	6.25	6.9
Fasting plasma insulin (0–30 mIU/l)	4.8	5.4	5.2
Blood karyotyping (banding)	46,XY	46,XX	46,XY

6,900 live births. Reports from the Middle East also confirmed clustering of BBS among many Bedouin tribes [14]. Such an apparently high frequency of BBS, as well as other autosomal recessive disorders observed among Bedouins could be attributed to the high existence of such genes in this population [14, 34] and increased rate of consanguinity and large family size. Talaat [11] found a consanguinity

rate of 87% in patients with BBS as compared to consanguinity rate of 54% among Kuwaitis [35].

The 3 newly ascertained Bedouin children with BBS in the present study were born in the Jahra area where multigenerational practice of consanguineous marriages and plethora of autosomal recessive disorders [14, 17] are predominant. Their diagnosis was based on the

Table 3. Female structural genital abnormalities in BBS

Case	Genital findings in affected individuals	Reference
1	Hypoplastic tubes, uterus, and ovaries	McLoughlin and Shanklin [18]
2	Uterus duplex, vaginal septa	McLoughlin and Shanklin [18]
3	Vaginal atresia with hematocolpos	Klein and Amman [16]
4	Vaginal atresia, urogenital and vesicovaginal fistulas	Nadimi et al. [19]
5	Hypoplastic uterus, absent right ovary, small left ovary	Campo and Aaberg [20]
6	Vaginal atresia	Srinivas et al. [21]
7	Vaginal atresia with hematocolpos	Cramer et al. [22]
8	Vaginal atresia with obstruction and dilatation of collecting system	Cramer et al. [22]
9	Urethrovaginal fistula	Cramer et al. [22]
10	No vaginal orifice	Green et al. [23]
11	No urethral orifice	Green et al. [23]
12	Vaginal atresia, urethrovaginal fistula and hydrometrocolpos	Stoler et al. [24]
13	Vaginal atresia, urethrovaginal fistula and hydrometrocolpos	Stoler et al. [24]

presence of 4 of the 5 clinical criteria: truncal obesity (81–95%), postaxial polydactyly (75–80%), mental retardation (70–85%), retinopathy (69–73%), male hypogonadism (74.4–85.7%) and female hypogonadism (45–53.1%) [10]. However, the BBS phenotype may be broader than the ‘classic pentad’. Different structural female genital anomalies were published in 13 patients with different ethnic background (table 3). Nephropathy and hepatic involvement were reported in several patients [25, 26].

Phenotype variability of BBS pleiotropic gene was manifested among the 23 patients ascertained in Kuwait and the 3 new patients in the present study (table 4). All subjects were born to healthy consanguineous parents in 16 unrelated families. All subjects have truncal obesity and mental retardation. The subjects revealed varying criteria: postaxial polydactyly (91.3%), night blindness (39.1%), retinopathy (47.8%), male hypogonadism (46.7%), female hypogonadism (12.5%) and renal problems (8.7%).

Visual impairment in BBS usually becomes apparent during the early teens with

rapid diminution of visual acuity and blindness by the age of 20 years (73.3%), with most patients being blind before the age of 30 [10, 19, 23, 27]. However, there were cases reported without obesity and mental retardation.

We cannot explain the gross truncal obesity on endocrinological basis in the 3 Bedouin children in the present study, since hormonal studies, carbohydrate intolerance, fasting plasma insulin and fasting blood sugar were normal. Their voracious appetite is mostly the causal agent. Hypogonadism is apparent in the 2 new male patients with possible eugonadotropic hypogonadism leading to micropenis, hypoplastic scrotum and cryptorchidism in the first patient, and micropenis in the second patient. The low plasma testosterone level in patient 1 suggests a defect in androgen biosynthesis affecting the testis. The 7-year-old female patient showed no structural genital anomalies after pelvic sonographic assessment with low FSH and elevated LH. Her low level of FT₄ associated with upper normal TSH level suggests borderline hypothyroid condition, and she showed no clinical evi-

Table 4. Parental consanguinity and phenotypic criteria among 23 Arabs with BBS in Kuwait (16 families)

	Present study (n = 3)	Farag and Teebi [11] (n = 20)	Total (n = 23)	
			n	%
Parental consanguinity	3/3	13/13	16/16	100
Truncal obesity	3/3	20/20	23/23	100
Developmental delay and mental retardation	3/3	20/20	23/23	100
Postaxial polydactyly	3/3	18/20	21/23	91.3
Visual impairment				
Night blindness	2/3	7/20	9/23	39.1
Pigmentary retinopathy	2/3	9/20	11/23	47.8
Hypogonitalism ± hypogonadism				
Males	2/2	5/13	7/15	46.7
Females	0/1	1/7	1/8	12.5
Renal problems	1/3	1/20	2/23	8.7

dence of hypothyroidism, with no delayed linear growth and appropriate bone age to chronological age.

There is no apparent explanation for the hypertension (190/120) elicited in the first patient, which is more than 2SD for his age with normal serum electrolytes, renal profile, serum cholesterol, thyroid function tests, serum aldosterone, plasma renin activity and urinary catecholamines. Renal biopsy was not done. The possibility of renovascular disorder has to be excluded.

Head CT scan studies of the 3 new BBS children showed cortical atrophy ± ventricular dilatation. Magnetic resonance study of the other BBS cases previously reported by Farag and Teebi [11] is highly beneficial since results of previous biochemical, radiological and pathological studies do not support the previous suggestion of associated hypopituitarism, diencephalic or hypothalamic disorders.

Recently linkage studies with the highly polymorphic DNA markers have mapped at least 3 BBS loci to the long arms of chromosome 3, 11 and 16 [28–31]. In a large Bedouin

family significant linkage was shown with chromosome 3 locus [32]. In another Bedouin family, BBS locus was found linked to markers that map to 16q21 [30]. These data indicate locus heterogeneity among these Bedouin tribes. Nonallelic genetic heterogeneity is further documented by finding 2 more loci causing BBS on chromosome 11 and 15 [28, 33]. Phenotypic variability was evident comparing three unrelated Bedouin kindreds, and which were used for linkage mapping of BBS loci on chromosomes 3, 15, and 16 [33]. Such genetic heterogeneity is a clue for the inter- and intrafamilial phenotypic variability of the BBS pleiotropic gene.

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