Two sisters with Bardet-Biedl syndrome: brain abnormalities and unusual facial findings

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Bardet-Biedl syndrome (BBS) is a rare autosomal recessive disorder with a wide spectrum of clinical manifestations. BBS is predominantly characterized by dysmorphic distal extremities, obesity, structural abnormalities or functional impairment of the kidney, rod cone dystrophy, and varying degrees of mental retardation. Hypogenitalism is also present, only in males, and in all cases, facial similarities. We present herein two sisters with BBS, one of whom also had cerebellar vermis hypoplasia and cerebral and cerebellar atrophy, and both of whom had ocular abnormalities in the form of epicanthus and telecanthus and metabolic syndrome. It should also be emphasized that the occurrence of cerebellar involvement such as cerebellar vermis hypoplasia and cerebellar atrophy in BBS is very unusual. The association of abnormalities in brain development and other facial features in children with BBS is not seen frequently; thus, these abnormalities should be searched carefully.

Key words: Bardet-Biedl syndrome, facial abnormalities, brain abnormalities.

Bardet-Biedl syndrome (BBS) is predominantly characterized by dysmorphic distal extremities, obesity, structural abnormalities or functional impairment of the kidney, rod cone dystrophy, varying degrees of mental retardation, and hypogenitalism limited to males[1-3]. Secondary features include speech delay and ophthalmologic abnormalities such as astigmatism, cataract, strabismus, nystagmus, myopia, and glaucoma. Other features, not always present, include hepatic fibrosis, diabetes mellitus, reproductive abnormalities, scoliosis, short stature, cardiovascular malformation, ataxia, dental abnormalities, and cerebellar dysfunction[4]. BBS in conjunction with brain abnormalities has been reported in only a few patients, and these abnormalities have included cerebellar atrophy and/or other cerebral abnormalities. This wide clinical spectrum is associated with genetic heterogeneity, since 12 genes (BBS1 to BBS12) have currently been identified[5].

The ocular anomalies can be isolated or part of a syndrome. In this report, we describe two sisters with BBS, one of whom also had cerebellar vermis hypoplasia and cerebral and cerebellar atrophy, and both of whom had ocular abnormalities in the forms of epicanthus and telecanthus. To our knowledge, ocular phenotypical abnormalities such as epicanthus and telecanthus have not been reported previously in BBS.

Case Reports

Case 1

A 16-year-old girl was referred to our clinic because of obesity and psychomotor delay. Her history revealed that her parents were close relatives, and that she had a sister with BBS (Case 2). She had polydactyly on both hands and feet. She had speech delay, and learning disabilities were noted at five years of age.

Her physical examination revealed the following: weight 90 kg (>97th percentile), height 157 cm (3rd-10th percentile), head circumference 57 cm (75th percentile), body mass index (BMI) 36.5 kg/m^2 (>95th percentile), blood pressure 110/70 mmHg, and heart rate 90/min. She had moderate mental retardation, brachydactyly and abdominal obesity. Facial features included long shallow

philtrum, thin upper lip, small downturned mouth, bitemporal narrowing, anteverted nares, telecanthus, and epicanthus (Fig. 1). Ophthalmologic examination showed mild optic pallor, cataracts, peripapillary chorioretinal atrophy, and peripheral localized pigmentation. Her pubertal status was consistent with Tanner 5, and she had regular menses.

Laboratory findings were as follows: fasting blood glucose (FBG) level: 100 mg/dl, insulin: 13.7 uIU/ml and homeostasis model assessment of insulin resistance (HOMA-IR): 3.34. Oral glucose tolerance test (OGTT) revealed impaired glucose tolerance, with 2nd hour glucose of 158 mg/dl and insulin of 54 uIU/ml. Plasma cholesterol level of 173 mg/dl, triglyceride (TG) level of 150 mg/dl and high-density lipoprotein (HDL) level of 29 mg/dl were indicative of metabolic syndrome. Other biochemical parameters were within normal limits. Tandem mass spectrometry and urine organic acid quantification were normal. Abdominopelvic ultrasonography, electroencephalography and echocardiography were normal. Renal scans were normal. Brain magnetic resonance imaging (MRI) showed cerebral and cerebellar atrophy and cerebellar vermis hypoplasia (Fig. 2).

Case 2

A 12-year-old girl was referred to our clinic because of obesity and psychomotor delay. Her elder sister had BBS (Case 1). Her history revealed extra digits on both feet and left hand at birth. She had speech delay (first words at 3 years) and learning disabilities.

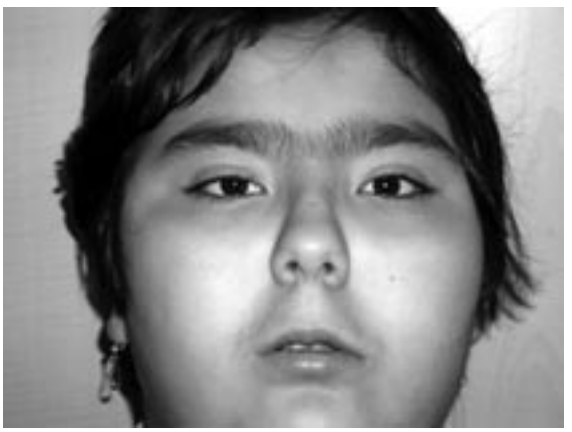

Fig. 1. Epicanthus and telecanthus in Patient 1.

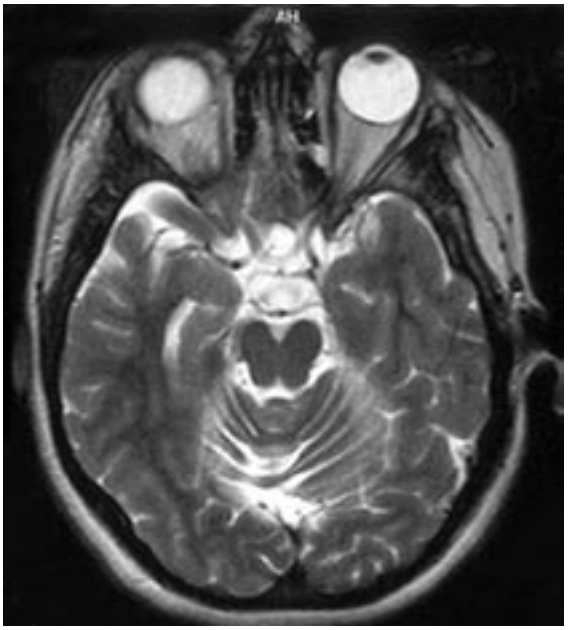

Fig. 2. Magnetic resonance coronal T2-weighted image of Patient 1 showing cerebral and cerebellar atrophy and cerebellar vermis hypoplasia.

Physical examination revealed the following: weight 66.5 kg (>97th percentile) and height 150 cm (3rd-10th percentile), head circumference 54 cm (75th percentile), BMI 31.6 kg/m^2 (>95th percentile), blood pressure 100/60 mmHg, and pulse 80/min. She had brachydactyly, moderate mental retardation and truncal obesity. Facial features were similar to those of her sister. The ocular examination showed peripapillary chorioretinal atrophy. The other ocular findings were mild epicanthal folding and telecanthus. Her pubertal status was Tanner 2.

Laboratory investigations revealed the following: FBG: 80 mg/dl, insulin: 15.1 uIU/ml and HOMA-IR: 6.02. OGGT revealed hyperinsulinemia (insulin: 228 uIU/ml). Plasma cholesterol level of 154 mg/dl, TG level of 228 mg/dl and HDL level of 27 mg/dl were indicative of metabolic syndrome. Abdominopelvic ultrasonography was normal. Renal scans, brain MRI, electroencephalography, and echocardiography were normal. Blood pressures in both patients in all four extremities were normal.

Discussion

The BBS is an autosomal recessive disorder characterized by clinical and genetic

heterogeneity[2,3]. The full spectrum of clinical features is found in only 40-45% of patients with BBS[1-6]. Both of our patients manifested brachydactyly, moderate mental retardation, chorioretinal atrophy, truncal obesity, and polydactyly, without renal involvement. These findings are associated with BBS diagnosis according to the revised criteria[2]. Only 60-70% of BBS patients have mutations identified in at least one of the 12 currently identified genes[5]. Several studies indicate that BBS1 (11q13) is the most common causative locus[2], but there are several families of Middle Eastern and Asian origin who do not show linkage to any known locus[3].

There are a few reports on the facial features of BBS. It was described that characteristic facial findings of BBS include brachycephaly, macrocephaly, microcephaly, large ears, short and narrow palpebral fissures, deep-set eyes, a flat nasal bridge with anteverted nares, hypertelorism, bitemporal narrowing, a long shallow philtrum, thin upper lip, and small downturned mouth, and frontal balding in adult males[2,3]. Most BBS patients are reported as having a typical facies of "moon face", frontal premature balding, enophthalmos, and downward-slanting palpebral fissures. These findings are characteristic when present; however, they are not necessarily helpful in all cases[2]. Both of our patients had facial features including long shallow philtrum, thin upper lip, small downturned mouth, bitemporal narrowing, and anteverted nares. Here, we report two BBS sisters who had epicanthus and telecanthus; these facial features have not been published previously in BBS. Although minor facial anomalies are distinguished from common variants by appearing less commonly than in 4% in the community, presence of both epicanthus and telecanthus in these two sisters with BBS is another unusual finding[6].

One of the sisters (Case 1) also exhibited the neurologic findings of cerebral and cerebellar atrophy and cerebellar vermis hypoplasia (Fig. 2). The literature contains very limited information about the association of cerebellar hypoplasia and cerebral atrophy with BBS. There are only six cases with BBS in the literature who had cerebellar atrophy[4,7,8]. To date, cerebral abnormalities reported in BBS cases included cerebral cortical atrophy, gyral atrophy, hydrocephalus, enlarged cerebral gyri, hemispheric asymmetry, temporal and parietal lobe hypoplasia, cerebellar vermis hypoplasia, frontal cortical dysplasia, enlarged 4th ventricle with mega-cisterna magna, and heterotopias[7,8]. Case 1 had both cerebral and cerebellar atrophy and cerebellar vermis hypoplasia, and the coexistence of these findings in one patient has not been reported to date in BBS, even in patients with brain abnormalities. However, our patient had a normal tandem gait despite the presence of cerebellar atrophy, as previously observed in a case report in the literature[4]. Beales et al.[2] reported that 40% of patients had ataxia with poor coordination and 33% had a gait abnormality in a series of 109 patients with BBS. Only 10 patients (9%) of the series had brain imaging (computerized tomography and MRI), and this failed to show any isolated structural abnormality of the cerebellum[2]. It has recently been proposed that the frequency of brain abnormalities in BBS may be higher than originally considered, since neuroimaging screening was not regularly performed in the previous cases. Rooryck et al.[8] reported that the progressive appearance of abnormalities in brain development may be suggestive of a degenerative process.

On the other hand, two patients also had metabolic syndrome (MES). MES has been rarely reported in BBS patients, which makes our patients more interesting[9]. Early detection and treatment of MES is important for reducing morbidity and mortality. We suggest that the most important step is a detailed physical examination, which together with modern imaging methods might be helpful in facilitating an early diagnosis of BBS. Ophthalmologists, endocrinologists and nephrologists should be aware of BBS because of its adverse prognosis with early onset of blindness, MES, increased vascular disease risk, and severe renal impairment.

In conclusion, our patients presented some important phenotypical features that were not previously described in BBS. In addition, it should be emphasized that the occurrence of cerebellar involvement such as cerebellar vermis hypoplasia and cerebellar atrophy in BBS is very unusual. The association of abnormalities in brain development and other facial features in individuals with BBS is not observed often in childhood and should be searched carefully.

Acknowledgement

The facial photograph of the patient was signed by the mother of our patient, giving written permission for its publication.

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