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Original

Renal features of Bardet Biedl syndrome: A single center experience

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Bardet Biedl syndrome (BBS), is a multisystemic disorder which is described as a ciliopathy. BBS is a rare autosomal recessive disorder and 21 different BBS genes have been defined to date. BBS is characterized with dysmorphic extremities, retinitis pigmentosa, obesity, hypogenitalism, intellectual disabilility and renal structural abnormalities. Renal symptoms in patients with BBS, are nonspecific and often undetected until end-stage renal disease. Here, we were reported 23 children with BBS (12 females, 11 males) with renal abnormalities from a single center and defined their features. Age at diagnosis were very variable (2 days-16 years). Median age at diagnosis was 84 months. Mean follow-up period was 42 months. All 23 children had urinary tract abnormalities on renal ultrasonography. These abnormalities were polycysts (34.8%), hyperechogenic kidneys (34.8%), fetal lobulation (21.7%), hypoplasia on at least one kidney (21.7%) and hydronephrosis in at least one kidney (17.4%). Vesicoureteral reflux and neurogenic bladder detected 11.1% and 22.2% of patients who recieved a voiding cystourethrogram, respectively. Proteinuria was found in 39 % of patients. Hypertension was defined in 21.7% of patients. Six of 23 children (26%) in our cohort had proven mutations in BBS genes. Five of them (83.3%) had homozygous mutations in BBS10 gene and one of them had homozygous mutation in BBS2 gene. All of 23 children had retinitis pigmentosa, twenty two of them (95.6%) had learning disabilities/cognitive impairment and seventeen of them (82.6%) had obesity. Renal involvement is now accepted as a cardinal feature and the most important factor causing mortality in BBS.

Key words: Bardet Biedl syndrome, children, renal abnormalities.

Bardet Biedl syndrome (BBS, OMIM 209900) is a multisystemic disorder which was described by Bardet[1] in 1920 and Biedl[2] in 1922. In 1866, Laurence and Moon[3] described four affected siblings with retinal dystrophy, obesity, and mental retardation. BBS is the standard term in common usage. BBS is a rare autosomal recessive disorder and 21 different BBS genes have been defined to date.[4,5] Molecular confirmation of the diagnosis for BBS can be acquired in about 80% over direct sequencing of the BBS genes.[6] The majority of pathogenic mutations are found in BBS1 and BBS10, accounting for 23.2% and 20%, respectively.[7] BBS is characterized with dysmorphic extremities, retinitis pigmentosa, obesity, hypogenitalism, intellectual disabilility, cardiovascular abnormalities, and renal structural abnormalities.[6] Renal malformations lead to end-stage renal disease which can be a major cause of morbidity, therefore it is particularly important to treatment renal abnormalities. The aim of this report was to analyze renal characteristic findings of 23 children with BBS, and define their renal features. To the best of our knowledge, although some studies were reported in the literature from national registries, this is the first study about BBS with only pediatric patients from a single center.

Material and Methods

This study was a single center and retrospective study. Twenty three children diagnosed with BBS, followed at our pediatric nephrology clinic, were enrolled in the study. All children with BBS are referred to our pediatric nephrology clinic in the presence of renal abnormalities. The height, weight and blood pressure measurements, patient age at the time of diagnosis, presenting symptoms, family history, renal functions which were included serum creatinine, urine protein:creatinine ratio and urine osmolality, BBS mutation analysis, ultrasonography, renal scans and voiding cystourethrogram (VCUG) were identified from patients' medical records. BBS was diagnosed with using the criteria of Beales based on clinical phenotyping.[8] Impaired urinary concentration was defined as the absence of an increase in the osmolality more than 750 mOsm/kg H_2O in the first morning urine. The estimated glomerular filtration rate (eGFR) was calculated using the Schwartz formula.[9] Non nephrotic range proteinuria was defined by spot urine protein to creatinine 0.2-2 mg/mg.

Genetic analysis were performed on only six of the 23 patients, other patients were diagnosed according to criteria of Beales.

We have customized next generation sequencing multigene panel (Qiaseq Panels, Qiagen, Germany) for BBS related genes via MiSeq System (Illumina). The coverage of the panels include all exons for each gene, at least 50 nucleotides upstream and downstream of each exon and 1 kb of both the 5' promoter regions and the 3' UTRs. The alterations identified were cross-referenced to the other samples within the same run as well as to a cumulative databases. After filtering the known SNPs, this comparison allows us to determine which changes are most likely novel and warrant further consideration. In-silico analysis for novel variants was carried out using SIFT, Polyphen2 and MutationTaster. All changes deemed of potential clinical relevance were confirmed by Sanger sequencing.

Data was analyzed using the SPSS statistical software (SPSS for Windows, version 17.0; SPSS Inc., Chicago, IL, USA). The data were expressed as means and standard deviation (mean±SD), median and range, number of patients (n) and percentages (%).

This retrospective study was approved by the Ethical Committee of Medical Faculty of Çukurova University (13.04.2018-76/2).

Results

Twenty three children who were diagnosed with BBS and had renal abnormalities were included in this study. Twelve of the patients were female (52%) and eleven of them were male (48%). The age at diagnosis were very variable. Median age at diagnosis was 84 (min:1-max:192) months. Mean (±SD) follow-up period was 48 (±46) months. Consanguineous marriage was documented in 70% (16/23) of all patients. Two pairs of siblings were included in this study.

Nineteen patients (82.6%) met four primary features, and four patients (17.4%) met three primary features with two secondary features from Beasles criteria. All children had urinary tract abnormalities on renal ultrasound examination. The urinary tract abnormalities in patients with BBS were polycysts (34.8%), hyperechogenic kidneys (34.8%), fetal lobulation (21.7%), hypoplasia on at least one kidney (21.7%) and hydronephrosis in at least one kidney (17.4%). Some of our patients had more than one renal abnormality on renal ultrasound examination (Fig. 1). Dimercaptosuccinic acid (DMSA) scan was performed on 9 (39%) patients who had history of recurrent urinary tract infections and all of them showed abnormal scan results. Abnormal DMSA findings in our patients were renal cortical scars, any focal uptake defects and decreased split renal function. VCUG was performed 9 (39%) patients. Vesicoureteral reflux was detected in one (11.1%) and

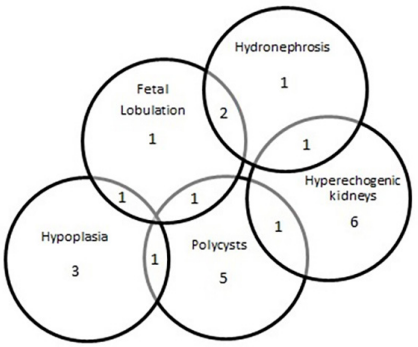

Fig. 1. Venn diagram showing the distribution of shared urinary tract abnormalities

Table I. Characteristic of Renal Findings at Time of Diagnosis.

Renal symptoms	n (%)
Impaired urinary concentrating ability	15 (65.2)
Proteinuria	9 (39.1)
Structural abnormalities	
polycysts	8 (34.8)
hyperechogenic kidneys	8 (34.8)
fetal lobulation	5 (21.7)
hypoplasia at least one kidney	5 (21.7)
hydronephrosis at least one kidney	4 (17.4)
Hypertension	5 (21.7)
CKD stage	
Stage 1 (eGFR>90 ml/min per 1.73m^2)	4 (17.4)
Stage 2 (eGFR:60-89 ml/min per 1.73m^2)	5 (21.7)
Stage 3 (eGFR:30-59 ml/min per 1.73m^2)	4 (17.4)
Stage 4 (eGFR:15-29 ml/min per 1.73m^2)	5 (21.7)
Stage 5 (eGFR<15 ml/min per 1.73m^2)	5 (21.7)
Vesicoureteral reflux	1 (4.3)

CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate

neurogenic bladder in two (22.2%) of the patients who receieved a VCUG. Non nephrotic range proteinuria was found in 9 (39%) of the patients. Hypertension was defined and treated in 5 (21.7%) of the patients. Non nephrotic range proteinuria with hypertension was observed in 2 (8.6%) of the patients.

Impaired urine concentrating ability was observed in 15 (65.2%) of the patients. History of polyuria was detected in 7 of the 23 patients (30.4%). At the time of diagnosis, four (17.4%) of patients had normal renal function and eGFR were found >90 ml/min per 1.73 m^2. Five of the patients (21.7%) had chronic kidney disease (CKD) stage 2, four of the patients (17.4%) had CKD stage 3, five of the patients (21.7%) were at CKD stage 4, and five of the patients (21.7%) were at the end-stage renal disease (CKD stage 5), at the time of diagnosis. Five patients (21.7%) with CKD stage 5 had anemia, metabolic acidosis, bone-mineral disease, hyperparathyroidism, and hypoalbuminemia at the time of diagnosis. The characteristics of renal findings at the time of diagnosis are shown in Table I.

Seven of the 23 (30.4%) patients needed renal replacement therapy (RRT) during their follow-up. Five of the seven patients (71.4%) were female. Three patients (13%) receieved hemodialysis treatment, three patients (13%) had a renal transplantation, one patient (4.3%) was started on peritoneal dialysis. Median age of patients at the start of RRT was 144 (min: 24-max: 204) months. All patients who required RRT, had polycystic kidney or renal hypoplasia. Only one patient with renal hypoplasia was at CKD stage 3 and this patient did not require RRT during the follow-up.

Seven of the patients (30.4%) were at CKD stage 1, five of the patients (21.7%) were at CKD stage 2, five of the patients (21.7%) were at CKD stage 3, two of the patients (8.6%) were at CKD stage 4, four of the patients (17.4%) were at CKD stage 5 at their last clinic visit. One of patients who was at CKD stage 5 at the time of diagnosis had undergone renal transplantation at the age of 5. She had normal eGFR and was defined as CKD stage 1 at her last clinical visit. Also, one of patients who had a renal transplantation at the age of 17, was at CKD stage 3 at the time of diagnosis and he was at CKD stage 4 due to treatment incompatibility at his last clinical visit. The third patient who had recieved a preemptive renal transplantation at the age of 10, was at CKD stage 1 at their last clinical visit.

The most common clinical features of patients were retinitis pigmentosa, developmental delay

Table II. Clinical Features of Patients with Bardet Biedl Syndrome.

Clinical features	n (%)
Primary	
Renal abnormalities	23 (100)
Red cone dystrophy	23 (100)
Learning disability/cognitive impairment	22 (95.6)
Postaxial polydactyly	21 (91.3)
Truncal obesity	19 (82.6)
Hypogonadism/genital abnormalities	4 (17.3)
Secondary	
Orodental abnormalities	11 (47.8)
Brachydactyly/syndactyly	10 (43.4)
Eye abnormalities	9 (39.1)
Speech delay/disorder	4 (17.3)
Hepatic involvement	3 (13)
Diabetes mellitus	2 (8.6)
Cardiovascular abnormalities	1 (4.3)

and cognitive deficit. Impaired glucose tolerance and/or insulin resistance were found in four of the patients (17.4%) while two of them had diabetes mellitus. The other clinical features of the patients are shown in Table II.

Six of the 23 children (26%) in our cohort had proven mutations in BBS genes. Five of them (83.3%) had homozygous mutations in BBS10 gene and one of them (16.7%) had homozygous mutation in BBS2 gene. Characteristics of BBS patients with proven mutations were shown in Table III.

Discussion

BBS is a rare autosomal recessive disorder which is currently considered as a ciliopathy. Immotile cilia function as sensory organelles and their defects are characterized clinically by retinitis pigmentosa, polydactyly, situs inversus, learning difficulties and cystic formation in kidneys, liver and pancreas. BBS is a disease of immotile cilia and defined as a ciliopathy.[6]

BBS prevalence varies from 1:160,000 to 1:18,000, in Europe and in Newfoundland, respectively.[10] Higher incidence in Arab populations can be due to high rates of consanguineous marriages. At least 21 gene mutations have been reported to be responsible for BBS (BBS1-21).[11] Forsythe et al.[11] reported that mutations in BBS2, BBS10, and BBS12 were more likely associated with severe renal disease than mutations in BBS1. Patients with BBS1 mutations are more likely to have early stage CKD.[11] In our study, six patients (26%) had blood samples for genetic analysis, five of them had mutations in BBS10 gene, and one of them had a mutation in the BBS2 gene. The earliest clinically diagnosed patient was the patient with the BBS2 mutation This patient had normal renal function with CKD stage 1 at the last clinical visit. Two patients with BBS10 mutation had end-stage renal disease, one of them was on hemodialysis treatment and the other had received a renal transplantation. Putoux et al.[12] reported that BBS10 gene mutations are associated with antenatal severe cystic kidney disease, which is incompatible with life. In contrast, in our study we did not have any policystic kidney disease in five patients with BBS10 gene mutation. As this study was a single center study, the number of patients were small and genetic analysis was not performed on all of these patients. Therefore, the genotype phenotype association of these patients has not been evaluated in this study.

The diagnosis of BBS is defined by clinical findings. Beales et al.[8] have suggested that the presence of four primary features or three primary features and two secondary features are diagnostic. Primary features are red cone dystrophy, postaxial polydactyly, truncal obesity, learning disabilities and cognitive impairment, hypogonadism in male or genital abnormalities in females and renal abnormalities; secondary features are speech

Table III. Characteristics of Bardet Biedl Patients with Proven Mutations.

Patient	Sex	Age at diagnosis (months)	Follow-up period (years)	Presenting symptoms	eGFR (ml/min per 1.73 m²)[a]	RRT[b]	Genetic analysis
1	Female	1	12	Hematocolpos, increased renal echogenicity and lobulated kidney, polydactyly, brachydactyly, retinitis pigmentosa	>90	No	BBS 2 p.Gyl88Alafs*6 (c.263delG) Homozygous
2	Female	72	10	polycystic kidney, polydactyly, brachydactyly, retinitis pigmentosa, obesity	29.9	Hemodialysis	BBS 10 p.Tyr177Cys (c.530A>G) Homozygous
3	Female	3,5	5	polycystic kidney, polydactyly, obesity, retinitis pigmentosa	20.6	No	BBS 10 p.Ala323Val (c.968C>T) Homozygous
4[c]	Male	36	7	polydactyly, polyuria, increased renal echogenicity, retinitis pigmentosa	>90	No	BBS 10 p.Thr516Asnfs*8 (c.1547delC) Homozygous
5[c]	Male	46	8	polydactyly, polyuria, increased renal echogenicity, retinitis pigmentosa	>90	No	BBS 10 p.Thr516Asnfs*8 (c.1547delC) Homozygous
6	Female	72	10	Polycystic kidney, Hematocolpos, polyuria, retinitis pigmentosa, brachydactyly	27.5	Renal transplantation	BBS10 c.2135_2138delAGAA Homozygous

[a]eGFR: estimated glomerular filtration rate, at time of diagnosis, [b]RRT: renal replacement therapy, [c]They are siblings

delay/disorder, developmental delay, behavioral abnormalities, eye abnormalities, brachydactyly/syndactyly, ataxia/poor coordination/imbalance, mild hypertonia, diabetes mellitus, orodental abnormalities, cardiovascular abnormalities, hepatic involvement, craniofacial dysmorphism.[8] All of our patients were diagnosed with these criteria.

Renal involvement is accepted as a cardinal feature and the most important cause of morbidity and mortality in BBS.[13] The renal phenotype is highly variable, ranging from cystic tubular disease, renal dysplasia, and focal segmental glomerulosclerosis to urine concentrating defects.[7] Guidelines for the management of patients with BBS suggest that every patient should have a baseline renal ultrasonography to detect for the presence of any structural abnormalities.[6] Renal malformations and impaired renal functions are present in 53-82% of BBS patients.[6,14] In a study of 156 children with BBS, renal ultrasonography was performed in 87 patients

and structural abnormality was found in 43 patients.[15] In another study, renal abnormalities were documented in 82% of the BBS cohort including 33 patients.[14] The presence of a structural renal abnormality is strongly associated with chronic kidney disease, however the presence of a renal abnormality does not mean that it will develop into chronic kidney disease. In accordance, all of our patients had renal abnormalities and CKD at different stages, while 17.4% of the patients at the time of diagnosis had normal renal function.

In a cohort study which the patients ranged in age from birth to 60 years old, 63% of BBS patients had normal eGFR or CKD stage 1, 37% of BBS patients had CKD stage 2-4, 5% of BBS patients had CKD stage 5.[15] In another cohort of 33 BBS patients, all aged>16 years (mean age 26.3 years), 36% of the patients had an eGFR<90 ml/min per 1.73 m^2, of whom 9% had moderate renal impairment (CKD stage 3 and 4).[14] In our study, only 17.4% of BBS patients were in CKD stage 1 at the time of diagnosis. In our opinion, this difference was due to the fact that these studies included all BBS patients, while our study only included BBS children with renal abnormalities.

Although renal abnormalities are nonspecific and often undetected until end-stage renal disease, polyuria/polydipsia is the earliest clinical symptom recognised in childhood. Urinary concentration defect has been reported to be present in approximately one-third of patients with BBS.[16] Sixty-five percent of our patients had impaired urinary concentrating ability at time of diagnosis. In contrary to the literature, in our study a high rate of impaired urinary concentrating ability was observed due to the presence of renal abnormalities in all of our patients.

Approximately 10% of BBS patients have end-stage renal disease and renal replacement therapies, including renal transplantation, are required.[6] In our study, 21.7% of patients had end-stage renal disease at the time of diagnosis, furthermore 7 of 23 patients needed renal replacement therapy during follow-up. Recents studies have shown that renal transplantation among BBS patients has good outcomes.[17,18] As we mentioned before three of the patients had undergone renal transplantation and had stable renal function (CKD stage 1) at their last clinical visit. In particular, steroid-free immunosuppressive therapy may be more appropriate due to the usual high body mass index among these patients.

In a case report, three of four BBS patients who were diagnosed in adulthood, were diagnosed as BBS after hemodialysis was initiated, and two of them were diagnosed with diabetic nephropathy and hypertensive nephrosclerosis. They mentioned that the prevalence of hypertension and diabetes mellitus in BBS patients may lead to misdiagnosis of the primary renal disease among end-stage renal disease patients with BBS.[19] Along with the fact that the cause of hypertension is not clear; it may be directly related to the mutant gene effect, vascular anomalies, renal parenchymal disease or obesity. In our study, 21.7% of the patients were diagnosed with hypertension and none of the patients had diabetes mellitus. Hypertension can be detected early in patients with BBS, while two thirds of all BBS patients had hypertension.[16] In a study, systemic hipertension was found in 36% of young adults with BBS and proteinuria was found 33% of patients, which could also be the consequences of long-term hypertension or diabetes.[14]

Our study has some limitations. This is a retrospective study from a single center and results have failed to demonstrate any genotype-phenotype correlation.

In conclusion, despite there being no curative therapy for BBS, early diagnosis is very important to improve quality of life, to control hypertension, for the management of obesity and to prevent progressive impairment of renal function. Regular ophtalmological assesment is also important. Children with BBS need multidisciplinary medical care. The renal abnormalities are the main life-threatening features because they can lead to end-stage renal failure and require renal replacement therapies.

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