

CASE REPORT

RENAL DYSPLASIA IN BARDET-BIEDL SYNDROME

Nadica Ristoska Bojkovska¹, Lidvana Spahiu², Aleksandra Janchevska¹, Zoran S. Gucev¹,
Velibor Tasic¹¹ University Clinic for Children's Diseases, Medical Faculty, Ss. Cyril and Methodius University, Skopje,
R. Macedonia² Pediatric Clinic, Clinical Center Prishtina, KosovoCorresponding Author: Nadica Ristoska Bojkovska, Sv.Kliment Ohridski 54 1/3 1000 Skopje, R. Macedonia;
Tel: +389 70 80 77 36; E-mail: nadicarbojk@yahoo.com**Abstract**

Background: Bardet-Biedl syndrome (BBS) is a multisystem genetic disorder characterized with central obesity, pigmentary retinopathy, polydactyly, mental retardation, and hypogenitalism. Renal abnormalities have been recognized as a cardinal feature of the disease with serious prognostic implication. The aim of this study was to analyze the renal status in children with BBS and to implement appropriate interventions in those with progressive course

Patients and methods: The diagnosis of BBS was established on the basis of criteria proposed by Beales et al. (J Med Genet 1999). Imaging of the kidneys and urinary tract was performed with ultrasound study, Tc99^mDMSA scan and a cystographic study. Twenty four hour urine collections were obtained for estimation of proteinuria and creatinine clearance. Blood pressure was monitored at clinical visits or as 24-hour ambulatory monitoring.

Results: There were 4 children (2 males, 2 females). All four children displayed abnormal kidney ultrasound and Tc99^mDMSA scan resembling dysplastic kidney(s). Two of them had overt proteinuria (glomerulo-tubular pattern). Three children had normal blood pressure and glomerular filtration rate (GFR): 107, 145 and 95 ml/min/1.73m², and the fourth had hypertension and progressive worsening of the GFR at 65 ml/min/1.73m². Conclusion: Children with BBS should undergo imaging studies of the kidneys and urinary tract at initial work up; in those with renal dysplasia proteinuria, GFR and blood pressure should be regularly monitored to slow down progression to terminal renal failure.

Key words: Bardet Biedl syndrome, renal dysplasia, chronic kidney disease, proteinuria, hypertension.

Introduction

Congenital anomalies of the kidneys and urinary tract (CAKUT) are significant cause of end stage renal disease (ESRD) in children and adolescents [1]. In a substantial cohort of patients CAKUT may be associated with less or more significant extra renal abnormalities. Bardet-Biedl syndrome (BBS) is ciliopathy – a multisystem genetic disorder characterized with central obesity, pigmentary retinopathy, polydactyly, mental retardation, and hypogenitalism [2–6]. Recently, renal abnormalities have been recognized as a cardinal feature of the disease

with serious prognostic implication. There is great genetic heterogeneity of the syndrome; so far 18 genes have been related to the pathogenesis of the BBS [7]. The sixteenth BBS locus (BBS16) was reported by Schaefer et al [8]. Interestingly, the carriers of this mutant gene presented with absence of polydactyly and fully penetrant association with early kidney failure. Therefore nephrologists should be familiar with this syndrome and its renal manifestations in order to diagnose nephropathy and implement appropriate therapeutic measures to prevent/retard progression to ESRD. In this work

we present the renal phenotype in a series of 4 Bardet Biedl patients who were evaluated at the Nephrology Service at the University Children's Hospital Skopje, for presence of CAKUT.

Patients and methods

The diagnosis of Bardet Biedel syndrome was established on the basis following clinical criteria:

The presence of four primary features or three primary features plus two secondary features [9]. The primary criteria are: (i) rod-cone dystrophy (ii) polydactyly (iii) obesity (iv) learning disabilities (v) hypogonadism in males and (vi) renal anomalies. The secondary criteria are: (i) speech disorder/delay (ii) strabismus/cataracts/astigmatism (iii) brachydactyly/syndactyly (iv) developmental delay (v) polyuria/polydipsia (nephrogenic diabetes insipidus (vi) ataxia/poor coordination/imbalance (vii) mild spasticity (especially lower limbs) (viii) diabetes mellitus (ix) dental crowding/ hypodontia/small roots/high arched palate (x) left ventricular hypertrophy/congenital heart disease and (xi) hepatic fibrosis.

In this work we present four Bardet Biedl patients who were evaluated at the Nephrology Service at the University Children's Hospital, Skopje, Macedonia in the period January 1st 2000-December 31st 2011 for the presence of CAKUT. This is the unique tertiary pediatric institution in Republic of Macedonia in which all children with syndromic CAKUT are evaluated. Careful clinical examination was performed by two clinical geneticists/dysmorphologists (A.J. and Z.G) and all 4 children met the mandatory diagnostic criteria for BBS. The initial imaging study was ultrasound evaluation of the kidneys and urinary tract with emphasis

on the echogenicity of the renal parenchyma, focal and global renal scarring, presence of hydronephrosis, and cysts.

If any of above mentioned abnormality was detected the patients underwent Tc99^mDMSA study and voiding urethrocytography.

Blood pressure was measured at the clinical visits and with 24 hour ambulatory monitoring. Standard biochemistry included hematology parameters, complete urinalysis, blood glucose levels, urea, creatinine, uric acid, electrolytes, lipid profile and liver enzymes. Twenty four hour urine collections were obtained for estimation of proteinuria (normal < 150 mg/d) and creatinine clearance (normal > 90 ml/min/1.73m²) using Schwartz formula.

Results

During the period January 1st 2000-December 31st 2011 four children were diagnosed as BBS according to the diagnostic criteria. There were two males and two females. Their clinical features are given in **table one**. All children had central obesity with body mass index ranging from 32.4 to 40.3 kg/m². Three children had congenital cardiopathies and one (with ventricular septal defect) underwent surgery. Three children also underwent surgery for polydactyly. All had visual problems and learning difficulties. Ultrasound examination showed abnormal pattern in all four children and they underwent further imaging studies. Patient No. 1 and 2 showed bilateral dysplastic kidneys with increased echogenicity of the parenchyma, loss of corticomedullary differentiation and irregular contour of the kidneys (Figure 1). Patient No 3 and 4 showed focal renal scarring (Figure 2). Voiding cystography did not show reflux neither other pathology in all four children.

Table 1

Clinical features of the Bardet Biedl patients

Patient	Age*	Gender	Retinopathy	Polydactyly	Obesity	Learning disabilities	Hypogonadism	Renal status	other
1	6	M	+	+	+	+	+	Bill. dysplasia	Strabismus, astigmatism, speech delay
2	3	M	+	+	+	+	+	Bill. dysplasia	VSD, speech delay
3	7	F	+	+	+	+	NA	Focal scarring	ASD
4	6	F	+	+	+	+	NA	Focal scarring	VSD, strabismus

VSD – ventricular septal defect; ASD – atrial septal defect, NA – not applicable, * Age at diagnosis



Figure 1 – Ultrasound image of a Bardet Biedl patient with bilateral renal dysplasia



Figure 2 – Tc99m-DMSA scan in a child with Bardet Biedl syndrome and focal scarring in the lower pole of the right kidney

We found that three children (patients No 2, 3 and 4) had normal GFR at 107, 145 and 95 ml/min/1.73m² respectively, and the fourth (patient No 1) had progressive worsening of the GFR from 88 to 58 ml/min/1.73m². Two patients showed proteinuria 435 and 790 mg/day, mixed glomero-tubular pattern according to sodium-dodecyl sulphate polyacrylamide gel electrophoresis. Patient No 1 had hypertension which was poorly controlled due to noncompliance to treatment. This patient had several strong factors for progression of his chronic kidney disease at the last follow up at the age of 18 years: hypertension, smoking, obesity, sedentary life

style, lack of physical activity, glucose intolerance and abnormal lipid profile.

Discussion

Beales et al reported a series of 109 BBS patients in which 57 patients (52%) were subjected to radiologic investigation of the urinary tract [9]. Nearly half of them (46%) were found to have any renal abnormality such as parenchymal or calyceal cysts, calyceal clubbing and blunting, fetal lobulation, scarring, dysplastic kidneys, unilateral agenesis, vesico-ureteral reflux, horseshow kidney and ectopic kidney. A significant percent of patients (11%) had detrusor instability requiring either continuous or intermittent self-catheterization. Six patients (four of them children) had chronic renal failure and four (two of them children) were transplanted.

In a French study of 33 young adults with Bardet Biedl syndrome 36% (12 of 33) of the patients had an eGFR < 90 ml/min per 1.73 m² while 9% (3 of 33) had eGFR between 30 and 60 ml/min per 1.73 m² [10]. Urine concentration defect after 12 hour overnight fasting was found in 63%. All patients underwent imaging studies (ultrasound in all, NMR study in 24/33) and abnormal renal development was found in 50% of the patients consisting of asymmetry, atrophy, dysplasia and cysts. Overall, renal function impairment, tubulointerstitial lesions of dysplastic type and/or impaired urinary concentration ability were evident in 82%. Although genetic testing was performed in all

patients clear genotype-phenotype correlation could not be established due to small numbers, but authors noticed that all patients with BBS10 and BBS12 mutations had more severe phenotype (CKD, metabolic syndrome) compared with carriers of BBS1 who had milder phenotype.

Deterioration of renal function in patients with BBS usually has slow, progressive course and becomes evident in adulthood. There are incidental cases of BBS patients presenting renal impairment very early in the life. Billingsley et al reported five patients with BBS without polydactyly who had early and severe renal disease and required transplantation. [11]. A Romanian boy presented with terminal uremia at the age of 4 when diagnosis of BBS was established and the patient commenced chronic peritoneal dialysis [12]. A 12 year old boy from India presented at the age of 12 with polyuria, polydipsia, anemia, and chronic kidney disease (stage 3). Detailed physical examination led to the diagnosis of BBS which had not been recognized until this admission. His renal function worsened and he underwent pre-emptive kidney transplantation [13]. An early renal failure was also reported in a 4 year boy with BBS with bilateral kidney dysplasia due to posterior urethral valves [14]. A BBS patient from Iran was also reported and he reached terminal renal failure in the first decade and required renal replacement therapy [15]. An interesting case of female with BBS and renal failure in the neonatal period was reported. The baby was born with vaginal atresia resulting in hydrometrocolpos, hydronephrosis and renal failure. After desobstruction her renal function normalized but at the end of the first decade she progressed to ESRD due to her underlying renal pathology [16].

In our series all four BBS patients presented with global/focal kidney dysplasia. One patient progressed to CKD 3. He had severe risk factors for progression of CKD such as smoking, hypertension, obesity, sedentary life style, and lack of physical activity, glucose intolerance, and abnormal lipid profile. In anecdotal reports it was shown that even diet modification and reduction of the body mass index may positively influence for preservation of renal function [17]. Unfortunately mental retardation in our patient and behavioural changes typical for adolescence lead to the non compliance with medical treatment and healthy life style. Pediatric nephrologists have great responsibility for early diagnosis of BBS and recognition of neph-

ropathy as a cardinal feature of the disease. Transition to adult nephrology units should be done adequately without interruption of complex and multidisciplinary care of these patients.

Conclusion

Bardet-Biedl Syndrome is a rare ciliopathy associated with several features including obesity, retinopathy, renal defects, polydactyly, learning disabilities, and hypogenitalism. Children with BBS should undergo imaging studies of the kidneys and urinary tract at initial work up; in those with renal dysplasia or other structural abnormalities blood pressure, proteinuria and GFR should be regularly monitored. Close follow-up for renal impairment in patients with Bardet-Biedl syndrome from an early age is highly recommended to prevent ESRD.

REFERENCES

1. Sanna-Cherchi S, Ravani P, Corbani V, Parodi S, Haupt R, Piaggio G, et al. Renal outcome in patients with congenital anomalies of the kidney and urinary tract. *Kidney Int.* 2009; 76: 528–33.
2. Guo D. F, Rahmouni K. Molecular basis of the obesity associated with Bardet-Biedl syndrome. *Trends Endocrinol Metab.* 2011; 22: 286–93.
3. Andrade L. J, Andrade R, França C. S, Bittencourt A. V. Pigmentary retinopathy due to Bardet-Biedl syndrome: case report and literature review. *Obes Rev.* 2002; 3: 123–35.
4. Iannello S, Bosco P, Cavaleri A, Camuto M, Milazzo P, Belfiore F. A review of the literature of Bardet-Biedl disease and report of three cases associated with metabolic syndrome and diagnosed after the age of fifty. *Ann Endocrinol (Paris).* 2008; 69: 463–71.
5. Rooryck C, Lacombe D. Bardet-Biedl syndrome. *Minerva Endocrinol.* 1998; 23: 83–92.
6. Iannello S, Fagone S, Grasso G, Ierna D, Meli S, Pennisi P, et al. A case of familial Bardet-Biedl syndrome (obesity, slight mental retardation, polydactyly, retinitis pigmentosa and renal failure) with insulin-resistant diabetes mellitus]. *Pediatr Res.* 2004; 55: 908–11.
7. M'hamdi O, Ouertani I, Chaabouni-Bouhamed H. Update on the genetics of bardet-biedl syndrome. *Mol Syndromol.* 2014; 5: 51–6.
8. Sheffield V. C. Use of isolated populations in the study of a human obesity syndrome, the Bardet-Biedl syndrome. *Trends Mol Med.* 2004; 10: 106–9.
9. Beales P, Elcioglu N, Woolf A, Parker D, Flintner F. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. *J Med Genet.* 1999; 36: 437–446.
10. Imhoff O, Marion V, Stoetzel C, Durand M, Holder M, Sigaudy S, et al. Bardet-Biedl syndrome: a study of the renal and cardiovascular phenotypes in a French cohort. *Clin J Am Soc Nephrol.* 2011; 6: 22–9.
11. Billingsley G, Vincent A, Deveault C, Héon E. Mutational analysis of SDCCAG8 in Bardet-Biedl syn-

- drome patients with renal involvement and absent polydactyly. *Ophthalmic Genet.* 2012; 33: 150–4.
12. Mihai C, Marshall J, Stoicescu R. Bardet-Biedel syndrome with end-stage kidney disease in a four-year-old Romanian boy: a case report. *J Med Case Reports.* 2011; 5: 378.
 13. Hooda A. K, Karan S. C, Bishnoi J. S, Nandwani A, Sinha T. Renal transplant in a child with Bardet-Biedl syndrome: A rare cause of end-stage renal disease. *Indian J Nephrol.* 2009; 19: 112–4.
 14. Valavi E, Ansari M. J, Ahmadzadeh A. Bardet-biedl syndrome in a child with chronic kidney disease. *Saudi J Kidney Dis Transpl.* 2009; 20: 454–7.
 15. Momtaz H. E, Amanati A. Continuous ambulatory peritoneal dialysis for a patient with Bardet-Biedl syndrome. *Iran J Kidney Dis.* 2008; 2: 237–9.
 16. Cherian M. P, Al-Sanna'a N. A, Ayyat F. M. Hydro-metrocolpos and acute renal failure: a rare neonatal presentation of Bardet-Biedl syndrome. *J Pediatr Urol.* 2008; 4: 313–6.
 17. Dervisoglu E, Isgoren S, Kasgari D, Demir H, Yilmaz A. Obesity control and low protein diet preserve or even improve renal functions in Bardet-Biedl syndrome: a report of two cases. *Med Sci Monit.* 2011; 17: CS12–14.

Резиме

БУБРЕЖНА ДИСПЛАЗИЈА КАЈ БАРДЕТ БИДЛ СИНДРОМ

Надица Ристоска-Бојковска¹,
Лидвана Спахију², Александра Јанчевска¹,
Зоран Гучев¹, Велибор Тасиќ¹

¹ Клиника за детски болести, Медицински факултет, Универзитет „Св. Кирил и Методиј“, Скопје, Р. Македонија

² Педијатриска клиника, Клинички центар, Приштина, Косово

Вовед: Бардет Бидл синдром (ББС) е мулти-системско наследно заболување што се карак-

теризира со централна дебелина, пигментна ре-

тинопатија, полидактилија, ментална ретардација и хипогонадизам. Бубрежните абнормалности се сметаат за кардинална црта на болеста и имаат сериозно прогностичко значење. Цел на оваа студија е да се анализира бубрежниот статус кај деца со ББС и да се спроведат соодветни мерки кај оние со прогресивен тек на болеста.

Пациенти и методу: Дијагнозата на ББС е поставена врз база на критериумите предложени од Beales и сор. (*J Med Genet* 1999). Приказ на бубрезите и уринарниот тракт е изведен со ултразвук, Тс99^mDMSA-скен и со цистиграфска студија. Дваесет и четири часовни примероци на урина се користени за проценка на протеинурија и креатинин клиренс. Крвниот притисок е мониториран во тек на клиничките прегледи или како 24-часовен амбулаторен мониторинг.

Резултату: Евидентирани се четири деца (две машки, две женски). Сите четири деца имаа абнормален ултразвучен наод на бубрезите, а Тс99^mDMSA скен покажа присуство на диспластични бубрези. Две деца имаа јасна протеинурија. Трите деца имаа нормален крвен притисок и гломеруларна филтрација (ГФ): 107, 145 и 95 мл/мин/1.73м², додека четвртото дете имаше хипертензија и прогресивно влошување на ГФ – 65 мл/мин/1.73м².

Заклучок: Деца со ББС треба да се подложат на радиографски студии на бубрезите и на уринарниот тракт при првичната обработка; кај оние со ренална дисплазија протеинурија, ГФ и крвниот притисок редовно да се контролираат со цел да се забави прогресија кон терминална бубрежна слабост.

Клучни зборови: Бардет Бидл синдром, бубрежна дисплазија, хронична бубрежна болест, протеинурија, хипертензија.