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Case Report

Renal Manifestation of an Adolescent Boy With Bardet-Biedl Syndrome

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ABSTRACT

Background and Aim: Bardet-Biedl syndrome (BBS) is a rare autosomal recessive multisystemic genetic disorder that may affect the centrosome and ciliary transport. Retinal dystrophy, obesity, extremity deformities, mental retardation, and renal and genital system anomalies characterize the disease. Renal involvement is a major cause of morbidity and mortality.

Case Presentation: We report the case of a 16-year-old boy with BBS who had a history of delayed diagnosis and features of glomerulonephritis leading to chronic kidney disease. He underwent a renal biopsy, which revealed focal segmental glomerulosclerosis (FSGS) from a histopathological study.

Conclusion: To our knowledge, only a few FSGS cases have been previously reported in pediatric patients with this syndrome. We wish to alert clinicians to a wide variety of renal abnormalities that can be observed in patients with this rare disorder and to provide multidisciplinary management of BBS.

Keywords: Bardet-Biedl syndrome, Chronic kidney disease, Focal segmental glomerulosclerosis

J Ped Nephrol
Journal of Pediatric Nephrology

Introduction

Bardet-Biedl syndrome (BBS) is a rare autosomal recessive disorder characterized by physical anomalies of the limbs, obesity, vision impairment, cognitive impairment, and irregularities of the renal and reproductive systems [1]. Additional associated manifestations encompass speech impediments, dental irregularities, anosmia, congenital heart disease, diabetes mellitus, and liver fibrosis, among others [1]. Renal failure is the primary cause of mortality in patients with this syndrome [2]. The prevalence of BBS is estimated to range from 1:140000 to 1:160000 in North America and Europe [3]. O'Dea et al. showed that 25% had an estimated creatinine clearance <70 mL/min of 36 BBS patients [2]. In a retrospective study, it was shown that of 350 BBS individuals, 45% of adults and 46% of pediatric BBS patients had chronic kidney disease (CKD) stages I-V, suggesting a high rate of kidney dysfunction in BBS subjects. Although some studies have shown that severe renal impairment occurs in a small fraction of patients, 6% and 8% of pediatric and adult subjects, respectively, were in CKD stages IV-V [4, 5]. In Bangladesh, definitive data on the prevalence of BBS are lacking. Many patients are undiagnosed due to the low occurrence and variety of symptoms. This article presents the case of a 16-year-old boy admitted to the Department of Pediatric Nephrology at Bangabandhu Sheikh Mujib Medical University (BSMMU). He presented with typical symptoms of BBS along with characteristics of atypical nephrotic syndrome and CKD. Renal biopsy revealed focal segmental glomerulosclerosis (FSGS), which is rarely associated with this syndrome [6].

Case Presentation

A 16-year-old boy was admitted to the Department of Pediatric Nephrology at BSMMU with complaints of polyuria and polydipsia since early childhood, along with gradual weight gain. According to his parents, he experienced delayed developmental milestones, such as walking at 2½ years and speaking at 4 years. He struggled at school due to learning difficulties and poor performance. His mother also mentioned his visual difficulties, especially at night, in the last one and a half years. He was diagnosed with type 2 diabetes mellitus two months ago.

A 16-year-old boy with symptoms of BBS, atypical nephrotic syndrome, and CKD was admitted to the Department of Pediatric Nephrology at BSMMU. His random blood sugar level was 33.5 mmol/L, hemoglobin (Hb) A1C was 19.4% and his serum electrolytes were normal. The patient was treated with oral antidiabetic medications and insulin.

He was the second child of non-consanguineous parents, born by normal vaginal delivery at full term. The patient's mother had a history of abortion, intra-uterine death, and stillbirth. There were no similar illnesses in any of the families. On examination, he showed signs of hypertension, obesity, hyperglycemia, acanthosis nigricans, polydactyly, high-arched palate, dysarthria and mild intellectual disability. His pubic and axillary hair were present and he had normal genital development.

The results of other systemic examinations were unremarkable. Investigations revealed:

Hb%: 9.5 g/dL (↓), mild normocytic normochromic anemia, serum creatinine: 2.30 mg/dL (↑) (estimated glomerular filtration rate [eGFR]: 27 mL/min/1.73 m^2, CKD stage IV), serum, urea: 101.8 mg/dL (↑), serum electrolytes: Na^+: 142 mmol/L, potassium (K^+): 4.8 mmol/L, chloride (Cl^-): 111 mmo/L, total carbon dioxide (TCO_2): 21.8 mmol/L, serum albumin: 30 gm/L (↓), serum parathyroid hormone (PTH): 191.1 pg/mL (↑) (normal: 18.5-88 pg/mL), serum calcium: 8.1 mg/dL (↓), serum inorganic phosphate (PO_4^{3-}): 4.3 mg/dL, serum thyroglobulin (Tg): 554 mg/dL (↑), serum cholesterol: 122 mg/dL, serum alanine transaminase (ALT): 13 U/L, random blood sugar (RBS): 38.4 mmol/L (↑), HbA1C: 18.5% (↑), serum testosterone: 3.26 nmol/L (stage V), serum follicle-stimulating hormone (FSH): 10.36 mIU/mL (stage V), serum luteinizing hormone (LH): 5.218 mIU/mL (stage V), serum thyroid-stimulating hormone (TSH): 3.62 µIU/mL, free thyroxine (FT4): 218.6 nmol/L.

His fasting plasma C-peptide level increased (4.6 ng/mL), and homeostasis model assessment (HOMA)-IR index also increased (3.68). These findings, along with those of acanthosis nigricans, suggest type 2 diabetes mellitus. Urine R/E showed protein: +++, sugar: +++, pus cell: 1-2/HPF, red blood cell (RBC): nil, ketone bodies: absent, 24-hour urinary total protein: 10.73 gm/day (↑).

Ultrasonography of the entire abdomen showed that both kidneys had renal parenchymal disease (right kidney 10.3 cm, left kidney 9.2 cm, increased cortical echogenicity, maintained corticomedullary differentiation). The liver and spleen were also enlarged with mild fatty changes (grade 1). Echocardiography results were normal. Renal biopsy indicated FSGS. Both eyes' color fundus photography showed signs of retinitis pigmentosa (Figure 1). These

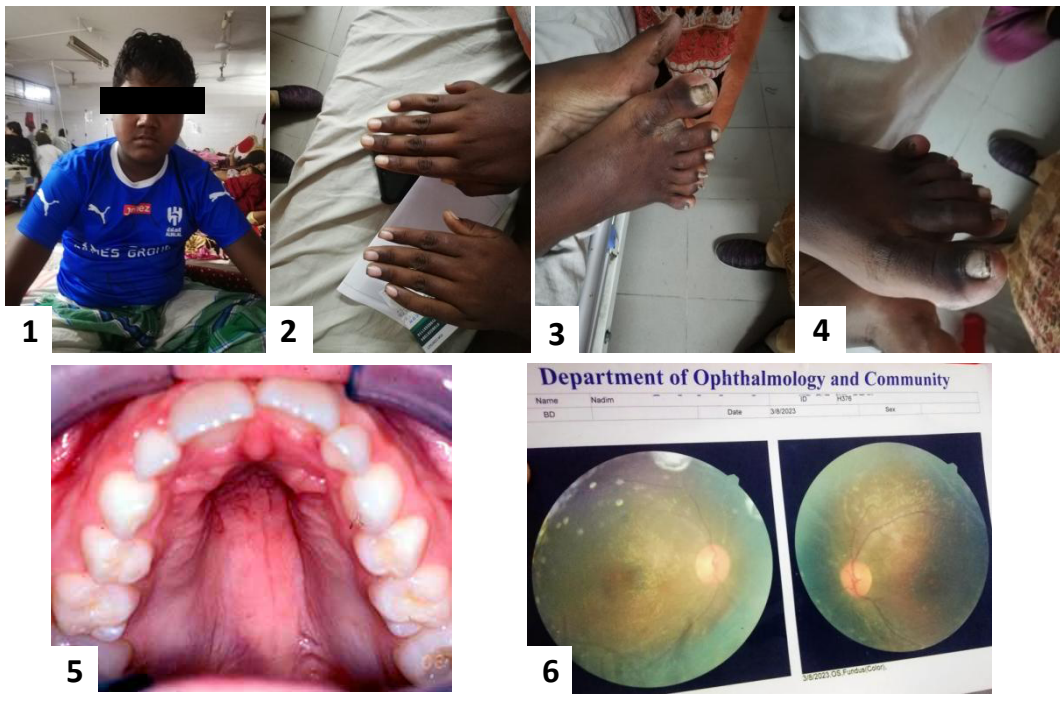

Figure 1. Different morphological features characteristic of Bardet-Biedl syndrome in our patient

2-4) Polydactyly in right hand and both feet, 5) High arch palate, 6) Color fundus photography of eye: Findings suggestive retinitis pigmentosa.

ophthalmological results were consistent with BBS. We planned to conduct comprehensive genome sequencing, currently unavailable at our hospital. Based on the overall clinical presentation, the patient was diagnosed with BBS due to the presence of five primary features (retinal dystrophy, polydactyly, truncal obesity, learning disabilities and renal malformations) and four secondary features (high-arched palate, delayed development, diabetes mellitus, speech disorder), as suggested by Forsythe and Beales (2013) [1]. He was treated with insulin after consultation with an endocrinologist, anti-hypertensive medications (angiotensin-converting enzyme [ACE] inhibitors), erythropoietin for anemia, fenofibrate for hypertriglyceridemia and other supportive management for CKD. After consultation with the ophthalmology department, the patient was treated with a cap. Vitamin A 50000 IU/day for 2 days every week and continued for the next 2 months, along with carboxymethylcellulose sodium eye drops: One drop on each eye every 6 hours, to be given continuously until further notice. He was also advised to undergo follow-up in the Ophthalmology Department after 3 months. The patient was provided with information and genetic counseling regarding this condition. The patient was scheduled for regular follow-up for further management. After a few days, the patient returned to the outpatient department for follow-up his blood glucose level was maintained, and anti-hypertensive drugs were adjusted.

Discussion

BBS is an uncommon autosomal recessive disorder. To date, 26 genes (*BBS1-BBS22*, *NPHP1*, *CEP19*, *SCAPER*, and *SCLT1*) have been found to play a role in the onset of this syndrome [7]. The full range of clinical symptoms typically develops by age 10, and the median age at diagnosis is 9 years [8]. Our patient's diagnosis occurred at 16 years old, indicating a longer delay than usual. BBS major criteria include rod-cone dystrophy (90%–100%), obesity (72%–92%), polydactyly (63%–81%), genital anomalies (59%–98%), learning difficulties (50%–61%), and renal anomalies (70%-90%). BBS minor criteria encompass speech disorders (54%–81%), developmental delay (50%–91%), diabetes mellitus (6%–48%), dental anomalies (51%), congenital heart disease (7%), brachydactyly/syndactyly (46%–100%), ataxia/poor coordination (40%–86%), cardiopathy (10%), deafness (11%–12%), and anosmia/hyposmia (60%). A diagnosis of BBS requires at least four major criteria or three major and two minor criteria [9]. Our patient exhibited five primary features (retinal dystrophy, polydactyly, truncal obesity, learning disabilities and renal malformations) and four secondary features (high arched palate, delayed development, diabetes mellitus, speech disorder), meeting the diagnostic criteria for BBS.

J Ped Nephrol
Journal of Pediatric Nephrology

However, the underlying pathology of BBS clinical findings is unknown. The study results of several subjects have suggested that this disease originates from basal body or cilia dysfunction [10]. Cilia are organelles resembling hairs that are present in almost all cells in the body. Cilia are divided into two groups: Motile and non-motile (primary). Non-motile cilia are thought to function as a sensory organelle in regulating signal transduction pathways. These primary cilia, which appear on the apical cell surface, mediate the transmission of mechanical and chemical stimuli via different signaling pathways [11]. Of 26 genes responsible for BBS, eight encode components of the BBS complex crucial in primary cilia homeostasis [7]. These defects in non-motile cilia have been clinically related to retinitis pigmentosa, polydactyly, situs inversus, learning difficulties, and kidney, liver, and pancreatic cystic diseases [12].

Our patient had visual difficulties in the past year, especially at night. A color fundus photograph of the patient's eye showed signs of retinitis pigmentosa (Figure 1). Rod-cone dystrophy is found in 90%-100% of cases of Bardet-Biedl syndrome [9]. This type of retinitis pigmentosa is characterized by an early decrease in visual acuity related to early macular involvement [13]. These ophthalmological findings were consistent with BBS. Mild non-proliferative diabetic retinopathy is characterized by microaneurysms with hard exudates and/or venous looping [14]. Proliferative diabetic retinopathy consists of one or more of the following: Neovascularization, vitreous or retinal hemorrhage [15]. Our patient showed no retinal changes, excluding diabetic retinopathy.

Renal abnormalities are common in these patients and are a major cause of death. The incidence of renal disease in this syndrome ranges from 70% to 90%. Uremia is probably the primary cause of mortality in 30%–50% of these patients [12, 16, 17]. Other studies have shown that the incidence of renal disease is lower than that mentioned above. Renal abnormalities are now considered a major diagnostic criterion for BBS. These include variations in kidney size, hydronephrosis, blunted calyces, parenchymal damage, pyelonephritis, atrophic tubules, chronic glomerulonephritis, cystic changes, renal hypoplasia and dysplasia, vesicoureteral reflux, mesangial proliferation, and sclerosis, interstitial fibrosis and tubulointerstitial diseases [12, 16, 18-22]. Harnett et al. [16] recently demonstrated the nature, extent, and severity of renal involvement in 20 patients with this syndrome. He observed that 50% of patients had hypertension; 3 had ESRD; 14/17 lacked urine-concentrating ability; 18/19 had calyceal clubbing, cysts, or diverticular, and 17/19 had fetal lobulations of the kidneys. Only 3 (15%) of the 20 patients had ESRD. These patients did not undergo renal biopsies.

Patients with BBS typically experience obesity and renal abnormalities [9]. Although approximately 90%-100% of patients with BBS present with renal involvement, cases of FSGS are sporadic [23]. Additionally, obesity is also associated with FSGS. Therefore, FSGS of the kidney may be caused by either BBS or obesity. The patient was managed by controlling blood pressure (ACE inhibitors for their anti-proteinuric properties), diabetes mellitus, advice on weight reduction, and other supportive management for CKD. In this patient, cyclosporine was not administered because its role in FSGS with BBS is not clearly mentioned in the literature, and cyclosporine may further worsen the already advanced stage IV CKD by promoting interstitial nephritis. The prognosis of this patient is guarded as the patient will eventually require renal replacement therapy.

The histological pattern of renal involvement varies in patients with BBS. Chronic interstitial nephritis, membranoproliferative glomerulonephritis, and ultrastructural changes in the glomerular basement membrane are commonly reported in literature [5, 18]. It is worth noting that FSGS has been rarely reported in these patients and should be recognized as one of the renal manifestations observed in this syndrome.

Conclusion

Patients with this rare, autosomal recessive syndrome exhibit various renal abnormalities. Every patient with this syndrome should undergo a thorough renal evaluation. If possible, patients with BBS with significant proteinuria, nephrotic syndrome, or impaired renal function should undergo a renal biopsy to better characterize and understand the degree of renal involvement in the patient and offer appropriate medical treatment.

Ethical Considerations

Compliance with ethical guidelines

Informed consent was obtained from the patient and his parents.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and manuscript drafting. Each author approved the submission of the final version of the manuscript.

Conflict of interest

The authors declared no conflict of interest.

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