Bardet-Biedl syndrome presented as chronic kidney disease with rare clinical associations in a Sudanese woman (case report)

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Abstract:

Bardet–Biedl syndrome is a rare autosomal recessive disorder falls under the spectrum of ciliopathy disorders. Its characterized by rod-cone dystrophy, renal malformations, postaxial polydactyly, learning difficulties, central obesity and hypogonadism. Hyponatremia, hepatic haemangioma, gall bladder stones and subclinical hypothyroidism rarely described in the literature as clinical presentations in BBS.

Key Clinical Message:

The Scarcity of BBS represents a challenge to diagnose it. The leading cause of death is renal impairment, so early detection of BBS is vital. Hepatic haemangioma and gallstones were rarely reported clinical features.

Key words:

BBS, chronic kidney disease, hyponatremia, hepatic haemangioma, subclinical hypothyroidism, gall stone, case report.

1. Background:

Bardet-Biedl syndrome (BBS) is a rare genetic disorder that affects multiple body systems. To date, twenty-one, disease-causing genes have been identified (BBS1-BBS21). Due to genetic heterogeneity, diagnosis of Bardet-Biedl syndrome is based on clinical features and family history. Laboratory investigations and imaging studies can be performed to assess the features that may help in the diagnosis.

The diagnosis of BBS is based on the presence of at least four major features or three major features and at least two minor features according to diagnostic criteria published by Beales et al [1]. Genetic analysis for confirmation of BBS is not available in most places, particularly in developing countries where many hospitals are resources-limited. The management of BBS is supportive through the multidisciplinary team approach. Genetic counselling of the family is important. The rarity of the syndrome and slow progression of it acts as a big challenge to early diagnose BBS. Late detection can result in an increased rate of morbidity and mortality. Chronic kidney disease (CKD) is a major contributor to morbidity and mortality among patients with BBS. Hepatobiliary involvement in BBS is diverse; however, hepatic haemangioma and gall bladder stone were rarely described in the literature.

In this report, we have represented a rare case of Bardet Biedl syndrome with hyponatremia as a first presentation of chronic kidney disease stage. Subclinical hypothyroidism, a gall bladder stone and hepatic haemangioma were found out during the workup. To the best of our knowledge, this is the first reported case of BBS in Sudan.

2. Case presentation:

A 38-years old Sudanese single woman, the fifth issue of a consanguineous marriage came to a university hospital, Sudan, complaining of irritability and vomiting. She had delayed developmental milestones while her siblings were normal. She had a poor school performance. At the age of six, the patient started to develop night blindness, and she has completely lost her vision at the age of 16. Her father also was blind and died due to ESRD. There was no history of diabetes mellitus or hypertension. Gynaecological history revealed that she had menarche at age of 14, and since then she has had irregular cycles. Timeline of her events was described in Figure [1].

On physical examination, blood pressure was 140/90 and pulse was 80 BPM, she had a puffy face and pendulous abdomen. Her body mass index was 31 kg/m2. Fundus examination disclosed retinitis pigmentosa and optic atrophy Figure [2]. Thyroid gland was not enlarged. Musculoskeletal system examination revealed postaxial polydactyly in the upper right limb Figure [3a] and bilateral lower limbs Figure [3b]. Her liver was

enlarged 4 cm below the costal margin, and bilateral lower limb oedema was noticed. Precordial and chest examinations were non-contributory.

Laboratory investigations showed serum sodium 110 mmol/L, blood urea 114 mg/ dl, serum creatinine 6.2mg/dl, haemoglobin 5.4 g/dl (normochromic normocytic anemia) and uncountable pus cells in urine examination. Thyroid function tests showed normal T3 and T4, with an increased TSH. RBS and LFT were normal. Other hormonal profiles showed features of hypergonadotrophic hypogonadism. [Table 1 for further details]. Study glomerular filtration rate (GFR) value based on 4 variables (age, race, gender, plasma creatinine) 8ml/min/1.73 m2.

Abdominal ultrasonography showed a small size right kidney (83*32mm) Figure [4a], while the left kidney was not detected. The liver was enlarged (16 cm) with hyperechoic focal lesion (picture of hepatic hemangioma) Figure [4b], solitary gall bladder stone, and infantile uterus. CT KUB revealed atrophied left kidney. Figure [4c] ECG showed features of LVH, transthoracic echocardiography revealed LVH, EF 62% and poor echogenicity.

Diagnostic challenges: CT with contrast and MRI abdomen to confirm hepatic haemangioma were not performed to avoid contrast-induced nephropathy and nephrogenic systemic fibrosis.

Differential diagnosis:

Alström syndrome , which is distinguished from BBS by the absence of polydactyly and preserved cognitive function.

McKusick-Kaufman syndrome , which is recognised from BBS by the absence of retinal disease, obesity, developmental disabilities and increased incidence of congenital heart disease.

Senior-Løken syndrome , which is marked from BBS by the absence of obesity, polydactyly, hypogonadism, and genitourinary malformations.

Laurence-Moon syndrome , which is distinct from BBS by presence of spasticity and absence of polydactyly

Our patient diagnosis was Bardet Bidel syndrome as she fulfilled all sex items of primary features (obesity, retinitis pigmentosa, postaxial polydactyly, renal abnormalities, learning disabilities and genitourinary malformations) in addition to two secondary features (developmental delay and left ventricular hypertrophy).

Treatment:

She received hypertonic saline (1 ml/ kg /hour) for 48 hours, proton pump inhibitor, in addition to fluid and salt restriction strategy. After 24 hours, her serum sodium rose to 119 mmol/L and after 48 hours, it rose further to 130mmol /L. Vomiting and irritability disappeared after 24 hours of starting the hypertonic saline. She also received injectable ciprofloxacin as her urine culture disclosed growth of E-coli. Besides, the patient has transfused three units of packed cell blood transfusion and received thyroxine 25 mcg OD and allopurinol 100 mg OD. Her readings of blood pressure were static at 140/ 90 for 3 consecutive days, so we decided to start ACEI (Lisinopril 2.5mg OD). Genetic counselling and the possibility of renal replacement therapy were discussed with her family.

Outcome and follow-up : Patient discharged in good conditions on day 5, her parameters of red blood cells were improved: HGB was 9 g/dl, and serum sodium 135mmol /L; she was discharged on erythropoietin, 1-Alfacalcidol, folic acid, iron, calcium carbonate, thyroxine, Lisinopril and allopurinol.

During her last follow up in Gezira hospital for renal disease and surgery, the patient was free of symptoms; her haemoglobin 11 /mg dl; blood urea was 70 mg/ dl and creatinine 3 mg/ dl. Her blood pressure 150/90, the dose of ACEI pushed up to 10 mg.

3. Discussion and Conclusion:

Bardet-Biedl syndrome (BBS) is a rare genetic disorder, which has an autosomal recessive pattern of inheritance. It has an estimated incidence of 1 in 150 000–160 000 in North American and European populations, but the incidence appears to be higher in areas with high levels of consanguinity [4]

Primary cilia play an important role in sensory perception and various signalling pathways; any defect in cilia can lead to disorders called ciliopathies. BBS falls under the spectrum of these disorders. Where the function of various ciliated systemic organs is disturbed, which results in systemic manifestations. The spectrum of BBS mutation varies; to manifest the disease some patients require three mutations. This genetic heterogeneity has made genetic analysis expensive and time-consuming as a result it was restricted to difficult cases and research studies. The diagnosis of BBS can be concluded by clinical criteria alone. Yet the underlying mechanisms that cause the disease are still not fully understood.

BBS is heterogeneous genetically, with 21 BBS genes (BBS1–BBS21) identified; the two main genes involved in BBS are BBS1 and BBS10, which are present in more than 20% of the cases. [5] Patients with mutations in *BBS1* generally present later than patients with mutations in *BBS10* , due to a milder phenotype and a later onset of retinal degeneration. BBS proteins localize to the centrosome and regulate the biogenesis and functions of the cilia.

The primary clinical features of BBS include rod-cone dystrophy, postaxial polydactyly, central obesity, cognitive impairment, male hypogonadism, complex genital anomalies and renal dysfunction [*6*]. The secondary features include speech disorders or delays, eye abnormalities like strabismus, cataract and astigmatism, brachydactyly or syndactyly, developmental delays, ataxia, Diabetes Mellitus, craniofacial dysmorphism, nephrogenic diabetes insipidus, hepatic fibrosis and left ventricular hypertrophy/congenital heart disease. [7] The presence of four primary features or three primary and two secondary features are required to diagnose BBS.

A wide range of renal abnormalities has been reported, including chronic renal failure, parenchymal cysts, calyceal clubbing, fetallobulation, renal scarring, unilateral agenesis, dysplastic kidneys, renal calculi and vesicoureteric reflux. The natural history of renal disease in BBS is still questionable. Renal impairment can be due to either primary causes(e.g., cystic renal disease) or secondary to hypertension, diabetes or metabolic syndrome. The most common cause of mortality among BBS patients is renal failure, as 25% of the patients die from it by the age of 44 [8]. Diabetes mellitus and hypertension are frequently observed in BBS patients than the general population, which can affect the progression of renal failure. The management of renal failure due to BBS is similar to any other cause. All three modalities of renal replacement therapy, i.e. chronic peritoneal dialysis, haemodialysis and renal transplantation can be applied in these patients. [9]

Hepatic involvement among BBS patients include peri-lobular fibrosis, periportal fibrosis, biliary cirrhosis, and bile duct proliferation with cystic dilatation to portal hypertension [10]. Hepatic haemangioma and gallbladder stones, as in our patient, are very rarely reported in the literature. Shrinkhalet al reported a case of BBS with hepatomegaly, where ultrasonography showed a hepatic haemangioma. [11] Gallbladder stones can be sought to be due to obesity.

Early diagnosis is important to guide the patient follow-up through regular assessment of renal function, blood glucose, weight, blood pressure, ophthalmic exams and imaging studies. To date, there is no curative treatment for BBS. Management of BBS requires a multidisciplinary approach team of paediatricians, nephrologists, orthopaedic surgeons, cardiologists, ophthalmologists, dental specialists, speech pathologist, and audiologists. Nephrotoxic drugs should be avoided, in addition toLifestyle modifications, which can help in reducing the BMI and preventingthe harmful consequences of obesity. TheUse of visual aids can improve patients' performance in their daily activities.Where as, for the cosmetic purposes, surgical removal of accessory digits can be applied. Learning disabilities may necessitate entrance to special schools and educational programs. Finally, genetic counselling can be of great benefit for affected individuals and their families.

In conclusion, BBS is a rare clinical syndrome, which may be passed undiagnosed by many clinicians. Renal impairment is one of the leading causes of death in the syndrome, so early detection of BBS is vital. The presence of postaxial polydactyly, blindness or learning disabilities in addition to renal malformations or

high renal profile should ring a bell about the possibility of BBS. Hepatic haemangioma and gallstones were rarely reported clinical features in BBS. The addition of these features to the secondary diagnostic features of BBS should be considered.

Abbreviations:

BBS: Bardet Biedl syndrome

ESRD: End Stage Renal Disease

BMI: Body Mass Index.

BP: Blood pressure.

TFT: Thyroid Function Test.

CKD: Chronic Kidney Disease.

LFT: Liver Function Test.

RBS: Random Blood Sugar.

ACEI: Angiotensin Converting Enzyme Inhibitor.

LVH: Left Ventricular Hypertrophy.

Declarations:

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Authors' contributions:

O E: The resident, who has diagnosed the case, the main writer of the article, participated in preparing the patient and responsible for the follow-up.

M A: Participated in preparing the patient and in the writing of the article.

A A: Participated in preparing the patient and in the writing of the article.

H Y: Responsible for clinical management.

M A: Participated in preparing the patient.

All authors have read and approved the manuscript.

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Consent for publication:

A written consent for publication has been obtained from the patient' brother.

Competing interests:

The authors declare that there is no competing interest.

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Figure legends

Figure [1] : Timeline described her previous events.

Figure 2 : Funduscopic picture showed pale optic disc and retinal pigmentation (retinitis

pigmentosa)

Figure 3 : **3a** right upper limb postaxial polydactyly,**3b** lower limb postaxial polydactyly.

Figure 4 : **4a** abdominal ultrasound showed small size right kidney 83*32 mm. **4b** abdominal ultrasound showed enlarged liver with hyper echoic focal lesion in segment V (features of hepatic hemangioma). **4c** CT-KUB showed atrophic left kidney.

Laboratory investigations	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Blood urea	165 mg/ dl (10-45)	145	120	110	90	84
Serum creatinine	6.9 mg/ dl (0.2-1.4)	6.8	6.6	5.4	5	4.2

Serum sodium	106 mmol/L (135-145)	110	119	130	135	135
Serum potassium	3.4 mmol/L (3.2-5)	3.5	3.8	4.8	4.5	4.2
Serum calcium	7.3 mg/ dl (8-11)					
Serum phosphate	5.5 mg/ dl (3.4- 4.5)					
PTH	454 pg/ ml (15-75)					
Hb%	6.4 g/ dl (10 - 12)					9
TWBCs	5.4 * 109/L (4.5-11.0)					
Ferritin	56 ng/ml (100-500)					
Transferrin saturation	14% (20-40)					
RBS	150 mg / 100 ml	130	135	140	150	140
HbA1c	5.9 %					
TSH	24 Uiu/ ml (0.5-5)					
T4	11 ng / ml (4-12)					
T3	1.2ng / ml (0.8-2)					
FSH	57 ng / ml (22-123)					
LH	65 ng /ml(11-40)					
Prolactin	44mg/ dl (5-35)					
UG	Uncountable pus cells					
Uric acid	13.3 mg/ dl (2.6-5.7)					
Serum cholesterol	154 mg /dl (up to 200)					
Serum triglyceride	145 mg /dl (up to 150)					

Table 1 : The table describes the laboratory investigations obtained for the patient during the course of the admission.

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