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Case Report

A Case Report of Bardet Biedl Syndrome in a Patient from Pakistan who Presented with Osmotic Symptoms associated with Diabetes Mellitus

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Abstract

Background: The primary features of Bardet Biedl syndrome (BBS) are characterized by retinal degeneration, central obesity, post-axial polydactyly, intellectual impairment, hypogonadism, and renal anomalies. The secondary clinical features are syndactyly, delay in the achievement of developmental milestones, diabetes insipidus, diabetes mellitus, congenital heart disease and liver involvement. It is diagnosed when a patient has either four primary or three primary and two secondary clinical features and the management depends upon those predominant features. **Case Presentation:** A 12-year-old boy presented with polyuria, polydipsia and polyphagia. His developmental milestones were delayed and had syndromic features on physical examination. Ultrasound of the abdomen and pelvis showed mild right-side hydronephrosis. His BMI was 28 and HbA1c was 18.3%, and values of LH and FSH were decreased. As a result, he was diagnosed with a case of BBS. He was commenced on insulin therapy with Insulin Regular (Human Insulin) and Insulin NPH (Human Insulin). **Conclusion:** Patients presenting with polyuria, polydipsia and polyphagia, along with the presence of syndromic features, should be assessed for BBS as osmotic symptoms associated with diabetes mellitus can be initial clinical presentation of BBS. Its management depends upon the signs and symptoms of the patient. Various options including weight loss, exercise, oral hypoglycemic drugs, and insulin are available to treat diabetes mellitus in BBS. Some cases can have very high levels of HbA1c on initial presentation, which may require insulin without trying oral hypoglycemic drugs to treat diabetes mellitus in BBS.

Introduction

Bardet Biedl syndrome (BBS) is an autosomal recessive ciliopathy, with a prevalence of 1 in 13,500 to 160,000 people.[1] It has primary as well as some secondary clinical features. The primary clinical features of BBS include retinal degeneration in 94%, central obesity in 89%, post-axial polydactyly in 79%, intellectual impairment in 66%, hypogonadism in 59%, and renal anomalies in 52% of patients.[2] Secondary clinical features of BBS include syndactyly, delay in the achievement of developmental milestones, diabetes insipidus, diabetes mellitus, and congenital heart disease.[3] It is diagnosed when a patient has either four primary or three primary and two secondary clinical features.[2] It is managed according to the signs and symptoms of the patient and requires a multidisciplinary approach.[4]

We present a case of BBS in a 12-year-old male, newly diagnosed diabetic patient who presented with polyuria, polydipsia and polyphagia. He had all the six primary clinical features of BBS. Among secondary clinical features of BBS, he had syndactyly, developmental delay and diabetes mellitus. The presence of osmotic symptoms of diabetes mellitus as a predominant feature of BBS and management of diabetes mellitus in BBS has been rarely discussed in the literature.[7]

Highlights:

- Patients presenting with polyuria, polydipsia, polyphagia along with the presence of syndromic features, should be assessed for BBS.
- The treatment options available treat diabetes mellitus in BBS include weight loss, exercise, oral hypoglycemic drugs, and insulin.

The Case

A 12-year-old boy presented to the outpatient department of Hayatabad Medical Complex, Peshawar, Pakistan complaining of polyuria, polydipsia, and polyphagia. According to the patient's mother, he was obese, had polyphagia and a low intelligence quotient (IQ) since childhood. For the past 6 weeks, he had increased frequency of urination, excessive thirst and increased appetite. He was born out of a non-consanguineous marriage through a normal vaginal delivery and was fully immunized. He started walking at 3 years of age and started speaking at 4 years of age. He was dropped out of school because of learning difficulties. . On examination, he had syndromic features including bilateral post-axial polydactyly in both of his feet *Figure 1,* syndactyly in his right hand *Figure 2,* widely spaced eyes, depressed nasal bridge, and high-pitched sound.

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Figure 1. **Bilateral Polydactyly.**

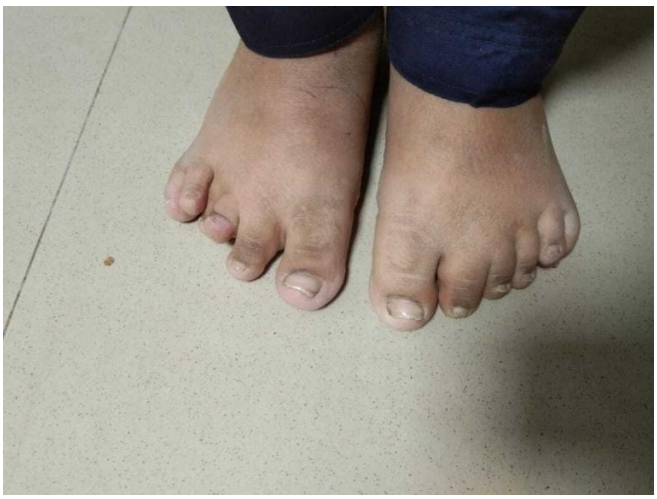
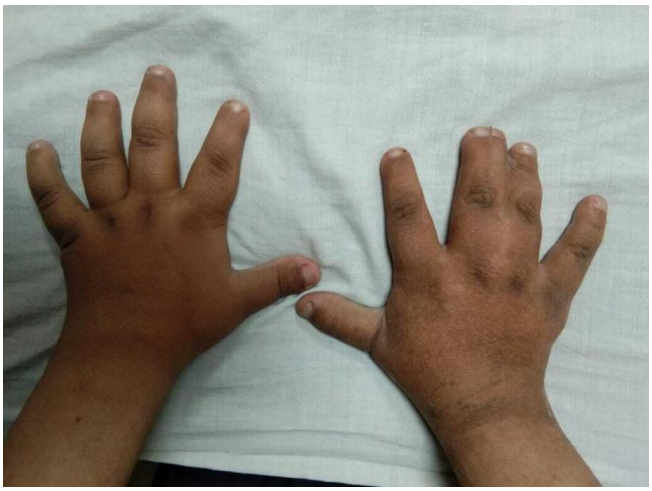


Figure 2. **Syndactyly in Right Hand.**



His body mass index (BMI) was 28. Head, ears, eyes, nose, and throat examination revealed bilateral conductive deafness and features of retinitis pigmentosa on fundoscopy. Central nervous system examination revealed no sensory and motor abnormalities. Genital examination revealed a small penis (<1cm), small and soft testis, and a redundant scrotum that was difficult to accommodate. The rest of the examination was unremarkable. Laboratory investigations done in the hospital are given below in *Table 1.*

Urinalysis and urine microscopy showed no abnormal laboratory values. An echocardiography was performed which was normal with no structural defects. Ultrasound of the abdomen and pelvis showed mildly enlarged spleen and mild right-side hydronephrosis. He was started on an injection of Insulin Regular (Human Insulin) 2 units three times a day and an injection of Insulin NPH (Human Insulin) 2 units in the morning and 4 units at night for the management of his high blood sugar.

Table 1. **Laboratory Investigations.**

Laboratory Exam	Result	Normal range	Unit
Sodium	132	135-150	mmol/L
Potassium	3.06	3.5-5.1	mmol/L
Chloride	77.8	96-112	mmol/L
Blood Urea	35	18-45	mg/dl
Creatinine	0.4	0.42-1.06	mg/dl
Total Bilirubin	0.3	0.1-1.0	mg/dl
Alanine Transaminase	13	10-50	IU/L
Alkaline Phosphatase	120	35-104	IU/L
Uric Acid	4.7	3.4-7.0	mg/dl
Glucose (Random)	360	70-140	mg/dl
T-3, Total	1.26	0.8-2.0	ng/ml
T-4, (Thyroxin)	11.48	5.1-14.1	ug/dl
Thyroid Stimulating Hormone	0.722	0.3-4.2	uIU/ml
Luteinizing Hormone (LH)	0.01	0.57-12.07	IU/L
Follicle Stimulating Hormone (FSH)	0.79	0.95-11.95	IU/L
Serum Testosterone	17.48	7-75	ng/dl for 12-16 years of age
White Blood Cells	10.5	4-11	$X10^3$/ul
Red blood Cells	4.55	4-6	$X10^3$/ul
Haemoglobin	11.9	11.5-17.5	g/dl
HbA1C	18.3%	4.5-7	%
Serum Calcium	9.2	8.5-10.5	mg/dl
Virology			
Hepatitis B surface Aantign(By ICT)	Negative		
Anti Heatitis C Virus (By ICT)	Negative		
Anti Human immunodeficiency Virus (By ICT)	Negative		

Legend: mmol/L: millimoles per litre; mg/dl: milligrams per decilitre; ng/ml: nanograms per millilitre; g/dl: grams per deciliter; IU/L:Iinternational units per litre; ug/dl: micrograms per deciltre; U/L: Units per litre; uIU/ml: micro-international units per milliliter; ng/dl: nanograms per deciliter; ul: microlitre.

Discussion

The prevalence of BBS ranges from 1 in 13,500 in some Arabian countries like Kuwait to 1 in 1,60,000 in northern Europe.[1] In Pakistan, the exact data regarding the prevalence of BBS is not available. Very few case reports have been reported of this disorder in Pakistan.[5] We report a case of BBS in a 12-year-old male patient from Peshawar, Pakistan who presented with polyuria, polydipsia, and polyphagia. He was diagnosed with diabetes mellitus and was later found to have met the clinical criteria for BBS.

The diagnosis of BBS is made on the basis of clinical signs and symptoms. It has six primary or cardinal features as well as some secondary features. The primary features of this syndrome include cone-rod dystrophy, obesity, hypogonadism, intellectual

impairment, renal abnormalities, and polydactyl.[3,6] Our patient had all of these clinical features. The presence of all the primary features of BBS in a single patient is rare.[7] Cone-rod dystrophy manifested in the form of retinitis pigmentosa on retinal screening He was overweight as his BMI was 28. Hypogonadism appeared in the form of small penis, small and soft testis, redundant scrotum, low levels of LH and FSH and low to normal level of serum testosterone. He was dropped out of school due to learning difficulties, renal involvement occurred in the form of right sided hydronephrosis and he had an extra digit in his both feet. Secondary features of BBS include, syndactyly, delay in the achievement of developmental milestones, diabetes insipidus, diabetes mellitus, and congenital heart disease.[3] Our patient had syndactyly in his right hand. He had developmental delay as he started walking at the age of 3 and speaking at age 4. He was newly diagnosed with diabetes as his random blood sugar was 360 mg/dl and HbA1c was 18.3%.

Our patient had dysmorphic facial features including widely spaced eyes, a depressed nasal bridge, and a long philtrum. These features have been described to be present in cases of BBS. Other facial features of BBS described in the literature but not present in our patient include high arched palate, reduced number of teeth, and retrognathia.[6,8]

BBS is inherited in an autosomal recessive manner. Mutations in twenty one different subtypes in the BBS gene can be responsible for BBS. As BBS is diagnosed clinically by the presence of either four primary clinical features or three primary and two secondary clinical features and does not require the confirmation of the presence of genetic mutation, we did not perform genetic testing on our patient.[2] Moreover, genetic testing was not feasible in our resource limited setting.

Very few cases of BBS with diabetes mellitus have been reported in the literature to the best of our knowledge. Quader et al.[9] described a case of Laurence-Moon-Bardet-Biedl syndrome (LMBBS) in a diabetic patient who presented with loss of vision, obesity, developmental delay and learning difficulties. Our patient was different than that as he initially presented with the osmotic symptoms of diabetes mellitus like polyuria, polydipsia, and polyphagia. On further evaluation, he was later on found to have primary and secondary features of BBS. This initial clinical presentation of BBS with osmotic symptoms is described in very few cases in the literature. Garg et al. also described a case of LMBBS with diabetes in a 22-year-old male patient. Though he presented initially with osmotic symptoms of polyuria and polydipsia, it was described to be an incomplete manifestation of LMBBS due to the lack of digital anomalies.[7]

The management of BBS requires a multidisciplinary approach, aligned with predominant signs and symptoms of the patient.[4] The predominant features in our patient were osmotic symptoms of diabetes mellitus. Diabetes mellitus in patients with BBS can be diagnosed using the guidelines of the American Diabetes Association (ADA).[10] A case-control study conducted by Mujahid et al. has shown that the patients with BBS are two times more likely to develop insulin resistance.[11] Therefore, the effective ways to treat diabetes mellitus in BBS could include exercise, weight loss, and insulin sensitizers including metformin and thiazolidinedianoes.[12] However, few cases of BBS have been reported which show resistance to oral hypoglycemic drugs as well and were ultimately started on insulin. A case report of BBS with diabetes mellitus was reported by Garg et al. in which the patient was resistant to oral hypoglycemic drugs and was consequently started on insulin.[7] Quader et al. also started a 13-year-old boy having BBS on metformin for the control of his diabetes mellitus but the data regarding his follow up and how effectively it controlled his diabetes mellitus was not given.[9] Our patient had very high level of HbA1c. The type of diabetes mellitus which affects the patients with BBS is mostly reported to be type 2 diabetes mellitus[6] and insulin administration is recommended for people whose HbA1C is greater than 10% or blood glucose levels more than 300mg/dl. [13] Apart from that, few patients have been reported to have no response to oral hypoglycemic drugs.[7] Due to these reasons, we started the patient on a basal bolus regime.

The prognosis of BBS is influenced by multiple factors. Patients may suffer functional impairment from progressive decrease in vision. In BBS, the leading cause of death is kidney disease but the life expectancy has been reported to be normal.[14] We arranged a follow up meeting with our patient to see the response to treatment and monitor the long term effects of BBS but he did not show up for follow up.

Summary – Accelerating Translation

Bardet Biedl syndrome (BBS) is a rare disorder which can affect eyes, kidneys, and can cause weight gain and intellectual impairment. It can also cause digital anomalies resulting in extra digits or fused digits. Apart from that developmental milestones can be delayed and a patient can have diabetes mellitus as well. This article describes a case of BBS in a 12-years-old boy and emphasizes the management of high blood sugar levels in BBS. He presented with increased frequency of urination, increased thirst, and increased appetite. His developmental milestones were delayed, he has low intelligence quotient, extra digits on his feet and fused digits in one of his hand. He had widely spaced eyes, depressed nasal bridge, and high-pitched sound. He also had a small penis, a small and soft testis and a redundant scrotum. Ultrasound of the abdomen and pelvis showed mild right-side hydronephrosis. His BMI was 28 and HbA1c was 18.3% and values of LH and FSH were decreased. He was diagnosed with a case of BBS. He was commenced on insulin for the treatment of his high blood sugar levels.

The initial clinical presentation of BBS may vary from person to person. Thorough examination and a high degree of clinical suspicion is required to diagnose it. Its management depends upon the signs and symptoms of the patient. Various options including weight loss, exercise, oral hypoglycemic drugs, and insulin are available to treat diabetes mellitus in BBS. Some cases can have very high levels of HbA1c on initial presentation, which may require insulin without trying oral hypoglycemic drugs to treat diabetes mellitus in BBS.

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