Bardet Biedl Syndrome: A Rare Case Report in a Tertiary Care Teaching Hospital, Dhaka, Bangladesh

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ABSTRACT

Bardet Biedl Syndrome (BBS) is an infrequent ciliopathic autosomal recessive genetic disorder that produces many effects and affects various body systems. Consanguineous marriage is conventionally considered as the most frequent etiology. The primary characteristics of the disorder are gradual visual impairment caused by retinal abnormalities, excessive weight gain, learning disabilities, Postaxial Polydactyly, Hypogonadism in males, renal abnormalities (kidney malformations and/or malfunctions). It affects both males and females. There is currently no specific cure for BBS but children with BBS benefit greatly from therapies like physical, occupational, speech and vision services. We, here, have presented a young boy of 15 years with the features of Bardet Biedl Syndrome.

Keywords: Bardet Biedl, Hypogonadism, Postaxial Polydactyly.
II. CASE PRESENTATION

A young boy of 15 years was admitted to Bangladesh Medical College Hospital with the complaints of excessive weight gain, poor vision at night, under development of genital organs. He was obese since first year of his life with increased appetite. Regarding his Birth history he was born out of a third degree consanguineous marriage. Throughout pregnancy his mother was completely fine and had no prescribed medications history at the gestational period. He was born by normal vaginal delivery at full term without any complications. History of asphyxia at birth, cyanosis, jaundice and breast feeding problems was negative. Immunization was done properly from time to time. According to his mother, he had delayed developmental milestones. He started walking at three years of age. He learned to communicate with others at the age of 4 years with a history of struggling in searching words. His parents enrolled him in a school, but due to difficulties in learning capabilities for low IQ in comparison to his other mates he eventually dropped out from there. His parents are in good health, as are his other siblings. One of his maternal uncles has suffered from the same indistinguishable illness like him.

On clinical examination, the boy had rounded face with double chin, bilateral gynecomastia, and pendulous abdomen Fig. 1. His height was 148 cm and weighted 70 kg (BMI 31.96 kg/m²) which was greater than 95 percentile according to his age. His testicular volume was found 1.5 ml and the measurement of stretched penile length (SPL) was 2.5 cm. Acanthosis nigricans was present in the axillary and neck region Fig. 2. Overall skin texture was coarse, thick, and dry. All of his 4 limbs contained extra axial polydactyly Fig. 3 & 4. Neurological evaluations revealed no abnormalities. Retinitis Pigmentosa was found in Fundoscopy.

Investigations including Complete blood count, urine analysis, chest X-ray, ECG and echocardiography were normal. Hearing assessment was normal. Biochemistry revealed his liver enzymes were elevated (AST 163 U/L, ALT 121 U/L, Serum total bilirubin 0.7 mg/dl and alkaline phosphatase 388 U /L). According to his serum creatinine level mild renal impairment was observed in his renal function tests (Serum creatinine 1.4 mg/dl, eGFR – 84.98 ml/ min/1.73 m²). Fasting lipid profile revealed elevated levels of triglyceride (TG) - 196 mg/dl and decreased level of High Density Lipoprotein (HDL) - 28 mg/dl. Abdominal ultrasonography revealed hepatomegaly with fatty changes in liver. His hormone analysis revealed serum TSH 10.09 uIU/ml, FT4 13.54 pmol/L (Primary Hypothyroidism), serum Luteinizing Hormone 0.07 mIU/ml and Serum testosterone 0.26 ng/ml (Secondary Hypogonadism). His oral glucose tolerance test showed fasting blood glucose was 4.6 mmol/L (Normal ≤ 7 mmol/L) and 2 hours after 75 gm glucose was 9.8 mmol/L (Normal < 11.1 mmol/L). His serum cortisol level was normal. We diagnosed the case as BBS as our patient had 4 primary features along with 2 secondary features (Table I).

There is increased number of innovations regarding genome analysis and sequencing on BBS genes. Currently, we have 21 studied BBS genes (BBS1–BBS20 and NPHP1) [7] but research on further gene analysis is still going on to know its complexity.

As currently no particular therapeutic treatment is available for this genetic disease, but that does not mean that there is nothing can be done to help people with BBS. Here, we provided treatment to our patient with symptomatic approach. Genetic counseling regarding the condition was done. We advised our patient with regular exercise at least 4 times per week and weight reducing diet chart was implemented. We prescribed him levothyroxine 50 microgram daily and metformin 850 mg once daily. After 3 months Ophthalmological follow up was scheduled and capillary blood glucose monitoring was advised. 4

Fig.1 Rounded face with double chin with bilateral gynecomastia.

Fig. 2 Acanthosis nigricans in the axilla.
primary features or 3 primary and 2 secondary features are required for a clinical diagnosis of BBS.[6]

| Primary features | Our case |
|------------------|----------|
| Rod-cone dystrophy (93%) | + |
| Polydactyly (63-81%) | + |
| Obesiy (72-92%) | + |
| Learning Disabilities (61%) | + |
| Genital anomalies (59-98%) | + |
| Renal anomalies (53%) | - |
| Secondary features | |
| Speech disorder/delay (54-81%) | + |
| Strabismus/cataracts/astigmatism | - |
| Brachydactyly/syndactyly | (6-100%)/k-95% |
| Developmental delay (50-91%) | + |
| Ataxia/poor coordination/imbalance (40-86%) | - |
| Spinal problem | - |
| Mild spasticity (especially lower limbs) | - |
| Diabetic nephropathy | - |
| Dental crowding/hypodontia/small roots/high arched palate (51%) | - |
| Congenital heart disease (7%) | - |
| Hepatic fibrosis | - |
| Anosmia/hyposmosa (60%) | - |

III. DISCUSSION

Bardet-Biedl syndrome is a heterogeneous autosomal recessive infrequent and intricate genetic condition which was entitled after Georges Louis Bardet, a French physician and Artur Biedl, a Hungarian Pathologist and Endocrinologist. With the blessings of modern genetic analysis among study population there 2 principal genes entangled in BBS are BBS1 and BBS10 and each of their presence has been observed in greater than 20% of the samples [8]. Bardet-Biedl syndrome is a heterogeneous autosomal recessive infrequent and intricate genetic condition which was entitled after Georges Louis Bardet, a French physician and Artur Biedl, a Hungarian Pathologist and Endocrinologist. With the blessings of modern genetic analysis among study population there is increased number of innovations regarding genome analysis and sequencing on BBS genes. Currently, we have 21 studied BBS genes (BBS1–BBS20 and NPHP1) [7] but research on further gene analysis is still going on to know its complexity. The 2 principal genes entangled in BBS are BBS1 and BBS10 and each of their presence has been observed in greater than 20% of the samples [8].

The mystery of comprehensive biochemical process that leads to BBS is still indecisive. Cellular ciliary structures are found to be defective in this genetic disorder for which it is a ciliopathy [8]. In 1886 Laurence and Moon reported the first known case and there was a debate in medical literature with the condition reported by Laurence and Moon, referred as Laurence-Moon syndrome (LMS). Moore et al came to a conclusion after 22 years of prospective cohort study of Newfoundland families that BBS and LMS are separate spectrum of same entity [9]. LMS is more out of the common condition than BBS. In LMS there are no polydactyly, patients usually present as progressive spastic para paresis, weakness is more in the distal than proximal limbs, along with mental retardation, visual problems in the form of retinal pigmentary degeneration and hypogonadism [10].

In Table I the essential and secondary characteristics of BBS have been described. For BBS the Diagnostic criteria are either four primary features or three primary and two secondary features. Four primary and two secondary features have been observed in our patient thus fulfilling the diagnostic criteria of BBS. One of the hallmark clinical features of this rare genetic disorder is visual impairment in the form of Retinitis Pigmentosa. Almost all patients present with the visual disturbance by second decade but presentation in the first decade of life is not uncommon. Macular involvement has been observed in this condition resulting in decreased visual acuity. With the prevalence of 72-92% depending on measurement criteria Obesity has secured the second vital characteristic feature in BBS. Obesity has been observed among these patients since childhood. Increased BMI is found with advancing age. It is usually noticed by their parents within the first 10 years of life in comparison to their other children and playmates of similar age [6]. Our patient was obese since childhood now has acquired fatty changes in his liver resulting in hepatomegaly. He had increased levels of TG and HDL along with increased BMI. The exact etiology of increased BMI is unrevealed; but increase appetite, lack of proper diet and physical activities seem to be responsible mainly [6]. One of the essential diagnostic criteria in BBS is Learning disability. Low IQ and various visual problems have encountered for this condition. Lately, only a minority of mentally retarded patients are determined by objective IQ tests. Around 44% of BBS cases have been found with an IQ level of 79 or below. Correlation has been made between the decrease IQ level and visual handicap [6],[11]. Our patient has both mental retardation and decrease visual acuity. Various forms and frequencies have been found in Limb deformities [6],[11]. The most popular forms of limb deformities are polydactyly (63-81%) and brachydactyly (6-100%) of both upper and lower limbs. The condition can be sometimes associated with prominent gap between the first and second toes, fifth finger clinodactyly and partial syndactyly [6]. Hypo-genitalism is reportedly more frequently in BBS males than females [6]. No renal abnormalities both morphological and functional had found in this case but there are various forms of renal abnormalities such as morphological (parenchymal cysts, dysplastic kidneys, calyceal clubbing), functional (chronic renal failure, renal calculi and vesico-ureteric reflux). 25% of BBS patients die by the age of 44 years due to Renal failure that is why it has become the utmost important cause of morbidity and early mortality in this genetic disorder [12]. Type 2 Diabetes mellitus has evaluated in 6 - 48% of BBS cases; occasionally Type 1 has also observed [12]. Our patient had impaired glucose level and he was advised by dietary measures and physical activities for weight reduction; diabetes mellitus was also observed by Haque M [13]. In our country a 12 year old boy with all the principal characteristics of BBS has developed Diabetes Mellitus according to the case report of Hussain et al [14].

As the diagnostic criteria of BBS are mainly clinical, so patients may remain in quiescent stage for many years until it has become flourished. Diagnostic dilemma has been found in some cases. Diagnostic difficulties arise when children born with no congenital abnormalities but
encountered problems with learning disabilities and excessive weight gain. Visual impairment brings the 1st attention of their abnormalities by the parents when they seek help from the physicians. For confirmation of diagnosis genetic testing may play a pivotal role but in a developing country like Bangladesh it is still very difficult to find its availability.

Multidisciplinary approach is needed for management of Bardet-Biedl syndrome. Both proper diet and exercise programs should be organized and scheduled to address Obesity, the most popular component of BBS. As Eye problems are of central concern so patients with BBS should be encouraged for periodic vision evaluation by ophthalmologic examinations and up-to-date their changing prescription lenses. Regular routine follows up should be arranged from time to time. Some of the physical abnormalities can be corrected with surgeries like, polydactyly for cosmetic purposes, and some genitourinary developmental anomalies and congenital cardiac conditions. As it is a genetic condition so Genetic Counselling may play a pivotal role in the management spectrum of the condition. Both the affected individual and his/her families should be encouraged for proper counselling by health professionals.

IV. CONCLUSION

Bardet Biedl Syndrome is a disease of genetic complexity. Physicians of all faculties should have resourceful information on BBS for spontaneous and accurate identification of the condition as it can be missed due to its scarcity. Many resourceful studies have been made about its complex pathophysiology but still a lot of more information need to be known. Patients may have good prognosis through careful evaluation and symptomatic management through multidisciplinary team although the disease is still incurable.

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