BARDET BIEDL SYNDROME – A RARE CASE REPORT WITH BILATERAL DOUBLE FUSED KIDNEYS

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Abstract: Background-Bardet-Biedl syndrome (BBS) is an autosomal recessive (AR) disorder exhibiting pleiotropy with involvement of multiple body parts or organ-systems. Its prevalence rate in India is not known. Characteristic features are retinitis pigmentosa (RP), obesity, polydactyly, hypogonadism, urinary system malformation, learning disability, etc. Here a unique case of Bardet-Biedl syndrome with bilateral fused double kidneys is discussed. Case presentation-A 9-year-old male child presented with the confirmed diagnosis of retinitis pigmentosa in the OPD. The parents were concerned about the vision and sought ayurvedic treatment for preservation of eye sight only, which was gradually getting worse. However, there were quite characteristic visible features that led to the detail interrogation and clinical examination, which ultimately helped in establishing the diagnosis of Bardet-Biedl syndrome. With observation of five primary features (RP, polydactyly, hypogonadism, learning disability and obesity) of BBS the child was evaluated further for possible renal malformation and detail hematology and biochemistry abnormalities. The KUB USG revealed bilateral fused double kidneys (on both sides) i.e. two PC systems, two ureters and two renal arteries on both the sides. These findings are unique and so far have not been reported in India.

Keywords: Bardet-Biedl syndrome, bilateral fused double kidneys, hypogonadism, postaxial polydactyly, retinitis pigmentosa, spatial dysgraphia.

INTRODUCTION
Bardet-Biedl syndrome (BBS) is an autosomal recessive (AR) disorder exhibiting pleiotropy with involvement of multiple body parts or organ-systems. Its exact prevalence rate in India is not known. Characteristic features are retinitis pigmentosa (RP), obesity, polydactyly, hypogonadism, urinary system malformation, learning disability, etc. Loss of vision is one of the major concerns for the patient and the family members. It starts with night vision loss. The patient gradually develops blind spots in the periphery of the visual field, which later merge to form tunnel vision. Here is a unique
case of Bardet-Biedl syndrome with bilateral fused double kidneys is discussed.

**CASE PRESENTATION**

A 9-year-old boy presented with the confirmed diagnosis of retinitis pigmentosa. The parents were concerned about his vision, which was getting worse with time passing. They did not give any complaint other than this. However, the external features of the child were very much convincing that main complaint of RP is associated with some other features and all together forms a specific clinical entity. The child was obese (central obesity) (figure 1) with weight more than 97 percentiles for the age and height about 80 percentiles for the age. He used to be less active as most of the time he felt lethargic and played in-door with his siblings. He had started abnormal weight gain since the age of about 6 months. Inquiry into his educational performance revealed that the child was a slow learner. There were complaints from the school as he could not copy simple sentences perfectly. In fact, this complaint led the parents for ophthalmic evaluation {scotopic and photopic electroretinography (ERG)}, which revealed that the boy had retinitis pigmentosa and his night vision was getting worse with time (figures 2a & figures 2b) showing initial ERG and figure 3 showing ERG after 6 months of diagnosis of RP). However, for some reasons the parents never consulted any neurology evaluation for his slow learning including delayed walking and speech nor did they try to find out the reason for his obesity and unexplained lethargy. There was no further clinical probe despite several consultations they have undergone for the child’s vision problem.

Figure 1. Central (truncal) obesity
Further interrogation disclosed that the child had 11 fingers (6 fingers on left hand with post axial polydactly) (figures 4a & b) and 12 toes (6 toes on each foot) (figure 5). Little fingers on both hands had elindactyly (figures 4a & b). His both feet were flat and had postaxial polydactly with one extra toe on each foot (figure 6). Right foot postaxial extra toe shows macrodactylism (figures 6). Psychosocial examination was insignificant. He avoided playing outdoor because most of the times he felt lethargic, which was attributed to his obesity by the parents. Genital examination revealed micropenis (stretched penile length or SPL was 3.8 cm, which was more than - 2 SD for his age[1] with small scrotum (for the age). Right testicular volume 1.5cm and left testicular volume 1.1cm. The testes were palpated and measured using scale after stretching the overlying skin in a warm room[2]. Both the testes were descended. The left testis was slightly smaller than right testis (figure 7). During further probe into his learning disability mother complained about his improper grip while writing and while copying the boy regularly missed alternate lines and sometimes a word or more within one line. However, the boy’s grip of pen was normal, but he had spatial dysgraphia (figure 8). His smell perception was normal.
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Figure 4(a): Six fingers Lt hand (post axial polydactyly) and clindactyly of little finger.

Figure 4 (b): Right hand shows clindactyly of little finger.

Figure 5: Post axial polydactyly of both feet (total 12 toes).

Figure 6: Both legs showing flat feet and right leg showing post axial polydactyly with macrodactyly of extra little toe.
The child was born to a non-consanguineous parents. Maternal antenatal care and the child’s natal history were uneventful. His birth weight was 3.0 kg, but he started gaining weight from the age of 6 months. The parents have induced good and healthy eating habit since the child had started gaining weight abnormally at a very young age. There was history of mild delayed developmental milestones of walking and speech. He lagged in the school performance.

There was no family history for any disorder involving learning disability or developmental delay. However, the child’s younger brother has congenital heart disease (some unspecified septal defect for which the reports were not available with the parents.
at the time of consultation of this teenager), but for this he had received treatment for more than a couple of years. The mother also had spontaneous abortion at 1-month gestation (between this patient and his younger brother).

Considering retinitis pigmentosa, central obesity, hypogonadism, polydactyly and learning disability with spatial dysgraphia the clinical diagnosis of Bardet-Biedl syndrome was beyond the doubt. For the diagnosis of this condition four primary features, or three primary features plus two secondary features are required (discussed in the latter part of the article). This child had five primary features and two secondary features before further hematologic, biochemical and radiologic investigations to rule out any other abnormalities were carried out, especially those related to urinary system. USG evaluation of the patient’s urinary system unfortunately showed bilateral fused double kidneys (on both sides) i.e. two kidneys with two PC systems, two ureters and two renal arteries on both the sides (figure 9), and both fused kidneys on both the sides having normal corticomedullary differentiation. The child’s renal and thyroid functions, and lipid profile were all within normal range.
Figure 9: USG KUB shows bilateral fused double kidneys (on both sides) i.e. two kidneys on with two PC systems, two ureters and two renal arteries on both the sides.

His hematologic and biochemical values were all within normal ranges as given here; Hb: 11.5gm/dL, TLC: 7,400; polymorphonuclear: 58, lymphocytes: 38; eosinophils: 02 and basophils: 02; blood urea: 17.0mg%; serum creatinine: 1.0mg%; blood uric acid: 4.9mg%; serum cholesterol: 120.0 mg%; triglyceride 86.0mg%; HDL: 40mg%; VLDL: 17.2mg%; LDL: 62.8mg%; serum sodium: 129.0mmol/L; serum potassium: 4.0mmol/L; serum chloride: 101.0 mmol/L; serum calcium: 9.0 mmol/L and serum PO4: 7.2mg/dL. His thyroid function tests were within normal range with T3: 1.57 ng/mL; T4: 10.9mg% and TSH mIU/L.

DIFFERENTIAL DIAGNOSIS

Laurence-Moon syndrome (LMS, also known as adipogenital retinitis pigmentosa syndrome): Progressive blindness, obesity and learning disabilities are common to this and BBS. However, the latter has polydactyly, which is not found in LMS.

Oliver-McFarlane syndrome (OMS): Like LMS and BBS, the patients with this condition also have progressive blindness, obesity and learning disabilities. However, these patients have abnormal growth of eyelashes and eyebrows (trichomegaly), which is not found in LMS and BBS.

Ellis-van Creveld syndrome (EVC, also known as chondroectodermal dysplasia): As the name suggests this is an inherited disorder of the bone growth. The patients with this condition have short stature with short arm and legs, polydactyly, malformed fingernails and toenails, dental abnormalities and partial atrioventricular canal defect. There is absence of RP so this condition can be easily ruled out.

Meckel-Gruber syndrome: This condition is very severe and is characterized by triad of large polycystic kidneys, postaxial polydactyly and occipital encephalocele. In most of the cases it is lethal (death before birth or shortly after birth). There is absence of retinitis pigmentosa in this condition. Also in BBS occipital encephalocele is not reported.

DISCUSSION

Bardet-Biedl syndrome (BBS, OMIM 209900) is clinically and genetically heterogeneous ciliopathy. It is inherited as an AR mode of pattern and is more prevalent in consanguineous populations than in nonconsanguineous populations. Its exact incidence in India is not known though till 2012 less than 15 cases have been reported[3].Multiple systems of the body may be involved. Truncal obesity (which starts
at a very young age), retinitis pigmentosa, postaxial polydactyly, hypogonadism, learning disability, renal malformation and/or malfunctions.

More than 20 different genes have been identified that are associated with BBS. However, clinical findings are sufficient to diagnose this condition. Diagnostic criteria have been developed for BBS. Presence of four primary features or three primary features along with two secondary features is diagnostic of BBS.

**Primary features**

- Retinal dystrophy (rod cone dystrophy)
- Post axial polydactyly
- Truncal obesity
- Renal abnormalities

**Secondary features**

- Hypogonadism (hypogenitalism)
- Learning disability
- Speech delay or disorder
- Developmental delay
- Craniofacial dysmorphism
- CVS anomalies
- Hepatic involvement
- Anosmia
- Ataxia
- Mild spasticity

Retinitis pigmentosa is one of the primary major features of BBS. Onset of loss of rods and cones in retina is gradual, but is not detected until the age of 7-8 years of age as this is the time when children with BBS start facing difficulty in their night vision or in the areas with dim light. The vision progressively gets weaker and by about middle half of the second decade of their life they are legally blind. In the beginning they lose peripheral vision (this type of vision is called tunnel vision) and then central vision. Retinitis pigmentosa follows a characteristic course of degeneration; starting with difficulty in night vision, followed by difficulty in discrimination of colors and then progressive tunnel vision.

Polydactyly is another primary feature characterized by presence of one of more extra fingers and/or toes. Extra finger or toe by the side of little finger or toe is called postaxial polydactyly. The other abnormalities involving fingers or toes may be syndactyly (fused fingers or toes) and brachydactyly (relatively shorter fingers or toes).

Truncal obesity denotes abnormal deposition of fat on the trunk area (in the abdomen and chest); with sparing of extremities. In 90% of patients with BBS the children are reported to be born with normal birth weight, but they start gaining weight in the first year of life.

Renal abnormalities or defects are highly variable. They may involve structure and function of the kidneys. Patients of BBS with renal malformation are at risk of developing end stage kidney disease and may require transplantation.

Hypogonadism in males is characterized by micropenis, undescended testis (cryptorchidism) or delayed puberty. The females may have underdeveloped organ/s of reproductive system, delayed puberty and often there may be irregular menses.
Among learning disabilities delay in achieving reading and writing skills are more common, which are not attributable to underlying visual impairment as the children start reading and writing much earlier than their cone-rod dystrophy starts. Abnormal neurological development may be responsible for poor cognition, coordination, delay in developmental and/or social milestones, etc. Anosmia (loss of sense perception) is also found in some of the patients.

More than 20 genetic mutations (e.g. BBS1, BBS2, BBS3, to BBS21, etc.) have been identified that cause BBS in majority of the patients. However, in some cases the mutation remains unidentified. Most of the mutated responsible genes identified for BBS are involved in encoding of cilia. Cilia are of two types; mobile and immobile. Immobile cilia are required for sensory processes e.g. light perception. Ciliary dysfunction is also considered to be responsible for renal abnormalities and anosmia also. However, for other clinical features the mechanism is not known.

What causes pleiotropy in BBS patients is not known, nor is known how the disease severity varies in different patients. However, there has been reports that mutation of BBS1 is associated with milder ophthalmic features of the disease while mutant BBS2, BBS3 and BBS4 are found to cause severe and classical forms of ophthalmic features of RP. Mutant BBS10 is reported to be involved in obesity and insulin resistance[4].

Diagnosis of BBS is based on the criteria developed for the purpose. As stated earlier this condition is pleiotropic and it may take some years for some of clinical features to come to light, hence the diagnosis also may take some years before it is confirmed. Majority of the times the child receives ophthalmic consultation for his/her worsening vision problem. Unfortunately, the attention is highly focused on this and there may be further delay in the diagnosis. Genetic diagnosis is available only in research laboratories and is financially a costly affair. Moreover, it is not mandatory to confirm the diagnosis through this, if clinical criteria are met for the purpose.

At present the treatment is only symptomatic. Regular ophthalmic evaluation is required to see the progress in vision abnormality. Similarly, regular monitoring of renal and cardiac function is also carried out so that timely medical intervention may be done in case of dysfunction of any of these vital organs. Hypogonadism may be properly dealt by an expert endocrinologist. Treatment of learning disability and CNS dysfunction including speech disorder should be started at the earliest possible so that education does not get affected. Proper diet plan (green gram dal, boiled and strained rice, whole wheat roti, seasonal vegetables and fruits; removal of heavy, left over, too sweet, stale, unctuous food, fish, curd, etc from the diet) and yoga sanas (such as halasana, ushtrasana, dhanurasana, naukasana, etc) as well as regular exercise may help control the truncal obesity to a certain extent. Shirshasana may be helpful in improving endocrinological functions and NS functions. Genetic counseling is recommended to all the patients afflicted with this condition.

Ayurvedic treatment is of much help in dealing with NS dysfunction, learning disability, speech disorder, dysgraphia, renal dysfunction (until the child develops
end-stage renal disease), truncal obesity, etc. Abhyanga and swedana are useful in NS dysfunction, delayed motor development, learning disability and dysgraphia while brahmighrita, shankshapushpi, vacha and other medhya rasayanas are useful in learning disabilities, poor academic performance, etc.

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CONFLICT OF INTEREST
No academic or financial conflict of interest.

CONSENT
A written consent was obtained from the parents of the patient for photography of the defects and also to publish the article without revealing the name or identity of the patient anywhere.

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