Bardet-Biedl Syndrome- Polydactyly with Multifarious Defects - A Rare Case Report

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PRESENTATION OF CASE

A 21-year-old Indian woman presented to the Emergency Department with symptoms of New York Association Class 2 dyspnoea for the last 3 weeks, pedal oedema of 2 weeks duration and decreased urine output since 3 days. She was the first born child of a nonconsanguineous marriage. She has a younger brother (15 years of age and normal development). The perinatal period had been uneventful. She had equinovarus deformity at birth. Her developmental history was marked by delayed attainment of motor milestones and delay in speech. She underwent surgery for equinovarus deformity at the age of four. She had language deficits and poor schooling skill and she could study up to 12th standard and had written examination with helper. She developed difficulty in night vision around 6th year and completely dependable by 10th year. There was delay in development of her secondary sexual characters and she attained menarche at the age of 18. She had multiple hospital visits for hypothyroidism, which was detected since 10 years of age, now on thyroxin 150 mg daily, but the underlying disease was left undiagnosed. She was not detected to have hypertension in the past. Sudden worsening of breathlessness and bilateral pedal oedema with decreased urine output made her to present to our Hospital's Emergency department.

On examination she was 160 cm tall and weighed 78 Kg, with a body mass index (BMI) of 30.5 Kg/m^2. She was having night blindness with tunnelled vision, central obesity, round face, postaxial polydactyly (24 fingers: figures 1, 2 & 3). She had severe pallor, bilateral pitting pedal oedema, acanthosis nigricans and was having hypertension with Blood Pressure 220/130 mmHg, Respiratory rate 40/mt. Cardiovascular exam showing low volume pulse, Pulse Rate 108 beats/min., with auscultation of the chest showed bilateral crepitation and congestive cardiac failure features. The patient had poor breast development and hair over the genitalia was sparse. There was no organomegaly on abdominal examination. Neurological exam was normal. The fundus examination showed features of atypical Retinitis pigmentosa (figure 4).

Figure 1 and 2

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Investigations

Routine investigations showed hypoxia with features of pulmonary oedema, elevated TC 11300, Hb 7.3, elevated creatinine and urea while lipid profile and liver functions were normal. Urine analysis revealed 3g proteinuria /day. Ultrasonography abdomen showed bilateral grade III renal parenchymal changes with minimal proteinuria. Chest x-ray showed features of pulmonary oedema. Echocardiography showed severe Left Ventricular systolic dysfunction with left ventricular ejection fraction 30% and grade I diastolic dysfunction.

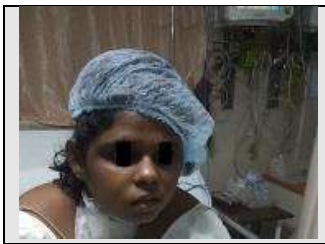

Figure 3

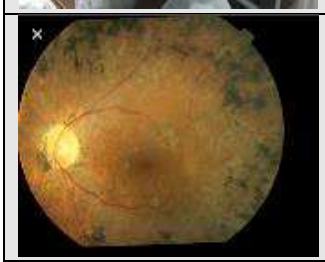

Figure 4. Fundus Picture of Atypical Retinitis Pigmentosa with Waxy Pallor

CLINICAL DIAGNOSIS

Bardet-Biedl syndrome with hypothyroidism, postaxial polydactyly, acute on chronic kidney disease, anemia, hypertension, congestive cardiac failure, atypical retinitis pigmentosa, learning disability and mental retardation.

DIFFERENTIAL DIAGNOSIS

Laurence-Moon Syndrome: it is a rare autosomal recessive genetic disorder associated with Retinitis pigmentosa, spastic paraplegia and mental disabilities, obesity and hypogonadism. But the presence of spasticity and absence of polydactyly differentiate it from the Bardet-Biedl syndrome.

Meckel-Gruber Syndrome: It is a rare, lethal, ciliopathic, genetic disorder characterized by occipital encephalocoele, large polycystic kidneys, postaxial polydactyly, hepatic developmental defects and pulmonary hypoplasia. This can be differentiated from BBS (bardet beidl syndrome) by the absence of Retinitis Pigmentosa and the presence of encephalocoele.

Ellis-Van Creveld Syndrome: Rare genetic syndrome characterized by short stature, short limb dwarfism, polydactyly, congenital heart defects. This can be differentiated from BBS (bardet beidl syndrome) by the absence of Retinitis pigmentosa, obesity and hypogonadism.

PATHOLOGICAL DISCUSSION

Bardet-Biedl syndrome is a ciliopathic autosomal recessive disorder consisting of obesity, retinitis pigmentosa, postaxial polydactyly, mental retardation, hypogonadism and renal dysfunction.[1] In 1866, Laurence and Moon[2] described retinal dystrophy, obesity, cognitive deficit and spastic paraparesis in four siblings of a family. Later Bardet[3]-Biedl[4] reported polydactyly as a separate feature in addition to the above mentioned and coined the term Laurence-Moon-Bardet-Biedl syndrome.

The disease is rare, with an estimated incidence of 1 in 150000-160000 in North American and European populations, but appears to be high in areas with a high prevalence of consanguinity.[5] Fewer than 15 cases have been reported from Indian subcontinent to date.[6] The disease has a slight male predominance of 1.3:1[1] with heterozygous[7] trait and was described under the group ciliopathy. The genetic heterogeneity makes the genetic analysis expensive and time consuming with its utility restricted to difficult cases or research studies, making it less effective in routine clinical practice, as diagnosis can be established by clinical criteria alone. But still genetic testing is important, as the mutation in Retinitis pigmentosa gene could be identified.[8] Gene therapy trials in mice with BBS (bardet beidl syndrome) (BBS4 and BBS1), thus has opened up new modes of targeted treatment.[9]

Beales et al[1] defined modified diagnostic criteria characterized by either four primary features or three primary and two secondary features clinically diagnose the disease (table 1) with Retinitis Pigmentosa, polydactyly and obesity. Postaxial polydactyly is a hallmark which clinch the disease diagnosis in a patient with blindness and obesity and also differentiate the disease from Laurence-Moon syndrome. The salient secondary features are congenital heart defects, dental anomalies, diabetes mellitus, diabetes insipidus, speech delay, brachydactyly and gait ataxia.

Primary Features	Secondary Features
Genital anomalies	Diabetes mellitus
Dental anomalies	**Developmental Delay**
Obesity	congenital heart disease
Polydactyly	Speech delay
Renal anomalies	Brachydactyly/syndactyly
Rod-cone dystrophy	Ataxia/poor coordination
Learning difficulties	Anosmia/hyposmia

Table 1

Beales et al[1] Criteria- Either four primary or three primary and two secondary features required to diagnose the disease. Our patients' positive findings are highlighted in Table 1.

According to Beales et al[1] study, aortic stenosis, patent ductus arteriosus and cardiomyopathies being more common in Bardet-Biedl syndrome and congenital heart defects less common; our study agrees with the above study. A study by Elbedour et al[10] and Moore et al, in 2005,

did not have cardiac canal defects in their patients with Bardet-Biedl syndrome. The supporting link between AVCD (atrioventricular canal disease) and polydactyly syndromes came to be known only after the molecular biology behind BBS (bardet beidl syndrome)were studied and in a study by Digilio et al,[11] it was found that AVCD (atrioventricular canal disease) was the prevalent heart defect. In the latest study by Imhoff et al[12] none of the patients had AVCD (atrioventricular canal disease) and our study was in par with the study as our patient's echocardiogram revealed no AVCD (atrioventricular canal disease). In report by Khan PA, Nishaat J et al[13] LMBBS patient born as a result of consanguineous marriage and presented with obesity, motor weakness and pain. This was evaluated by nerve conduction studies and was an important investigation in LMBBS. But in our study our patient's parents had non consanguineous marriage and the patient had presented with features of renal and cardiac failure other than motor weakness.

Echocardiography to look for potentially treatable cardiac disease is warranted and the radiological evaluation to look for renal anomalies is indicated in patients presenting with BBS (bardet beidl syndrome). Renal cell carcinoma screening must be done in patients with a positive family history or if the history is suspicious for a malignancy. Renal disease is one of the leading causes of death and leads to end-stage renal disease requiring renal replacement therapy. The basic management targets are obesity management, prevention of metabolic syndrome, screening for renal anomalies and for congenital heart defects and provision of visual aids.[14] The difficulty of making a firm diagnosis and lack of medical awareness contribute to the slow emergence of features such as Retinitis Pigmentosa and renal dysfunction, owe to the delay in the diagnosis of the condition and an early institution of therapy and surveillance.[15] The disease morbidity can be reduced by early screening for diabetes and its related complications, and avoidance of nephrotoxic drugs and selection of appropriate drugs. Blood pressure control with avoidance of volume overload should be the management in this patient with haemodialysis to prevent uraemia features. The treatment plan also involves an occupational therapist, a social worker and a psychologist. A significant improvement in quality of life can be achieved following the multidisciplinary teams as mentioned above.

DISCUSSION OF MANAGEMENT

The patient was treated symptomatically and underwent haemodialysis in view of anuria with features of uraemia and elevated renal parameters after nephrology consultation and a total of 2 haemodialysis was done. Pulmonary oedema managed with diuretics and noninvasive positive pressure ventilation, hypertension was managed with nitroglycerin drip and thyronorm 150mcg was continued. Cardiology consultation was done and advised to keep the patient on medical management for congestive cardiac failure. Ophthalmology consult was done in view of night blindness and was diagnosed atypical retinal pigmentation with dystrophy. Dyslipidemia was managed by consulting with dietitian and life style modification plans were advised. Supportive care was offered by involving occupational therapist, psychologist and social worker to improve the quality of life.

The patient's pedal oedema and breathlessness disappeared during her subsequent follow-up. His diuretics were optimized; she was doing fine and was under regular follow-up. She was told about the need for an annual echocardiogram. Her family members were counselled about the nature of this disease and its inheritance pattern, and also that consanguinity increases the risk of disease.

FINAL DIAGNOSIS

Bardet-Biedl syndrome with acute on chronic kidney disease, anemia, hypertension, congestive cardiac failure, hypothyroidism and retinitis pigmentosa.

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