End Stage Renal Disease, Differential Diagnosis, A Rare Genetic Disorder: Bardet–Biedl Syndrome: Case Report and Review

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Received: 4 September 2010 / Accepted: 16 January 2011 / Published online: 4 February 2011
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Abstract End stage renal disease (ESRD) represents a clinical condition in which there is an irreversible loss of endogenous renal function. Both structural and functional abnormalities of the kidney are associated with increased morbidity, mortality. Bardet–Biedel syndrome (BBS) is one of the rare genetic disorders with prevalence of 1 in 1,40,000–1 in 1,60,000 worldwide. ESRD in BBS patients is the final stage of the disease, increasing mortality in youth.

Keywords Bardet–Biedl syndrome · End stage renal disease · Differential diagnosis

Introduction

ESRD is due to progressive impairment causing irreversible damage to the kidney. Most common conditions that lead to ESRD are Glomerular disease (Ig A nephropathy), Renal artery stenosis, Systemic inflammatory disease (SLE, Vasculitis) and congenital/inherited disorders [1]. BBS is a rare autosomal recessive disorder, renal impairment frequently occurs in BBS, can lead to ESRD [2].

Case Report

On our routine delta checking of laboratory investigations, we found abnormal levels of serum urea (82.8 mg/dl), creatinine (8.8 mg/dl), uric acid (8 mg/dl), for a 16 year

old female. The patient's history is as follows, "A 16 year old female presented for management of ESRD, she was born to consanguineous parents, her parents noticed progressive decline in vision since the age of 5 years, presently she developed retinitis pigmentosa with blindness, she had delayed milestones, she is not a known diabetic/hypertensive. Attained menarche at the age of 14 years and had irregular menstrual history."

On Examination, she has pallor, polydactyly (left foot), dental anomalies, high arched palate. Cardio respiratory and abdominal examination does not reveal any abnormalities. Her vital sign are normal, waist circumference is 90 cm, BMI is 20. Fundus examination revealed rod–cone dystrophy (Retinitis Pigmentosa), ultrasonography revealed bilateral contracted kidneys and ovaries are not traced.

Laboratory investigations for fasting blood glucose, lipid profile, liver profile are normal. But there is alteration in serum urea (82.8 mg/dl), creatinine (8.8 mg/dl) and uric acid (8 mg/dl). Urine examination showed specific gravity of 1.030 and albumin trace. 24 h Urine protein is 1.9 g/day. With all the above clinical and laboratory finding it was diagnosed as Bardet–Biedl Syndrome.

Review

BBS is an uncommon autosomal recessive condition characterised by mental retardation, post axial polydactyly, obesity and pigmentary retinopathy [3]. Detailed biochemical mechanisms that lead to BBS is still unclear. 14 genes are responsible for the disease. The gene products encoded by these BBS genes are called BBS Proteins. BBS occurs throughout the world with ranging frequencies with prevalence rate of 1 in 1,40,000 to 1, in 1,60,000 in North America and Europe. Also occurs more frequently 1 in

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13,500 new borns in the Bedouin population of Kuwait, due to high rate of consanguinity [4]. In India only case reports have been described [5–8].

Criteria for Diagnosis and Pathophysiology

Based on the relative prevalence, the clinical phenotype was divided into major and minor features.

Major Features

1. Retinal dystrophy: Rod–cone dystrophy (Atypical Retinitis Pigmentosa) occurs in more than 90% of individuals with BBS [9]. Defect in the transport of photo-transduction proteins from the inner to outer segments of Photoreceptors leads to cell death and is thought to underlie the pathogenesis of retinitis pigmentosa in BBS [10].
2. Post axial Polydactyly: Polydactyly may involve all the four limbs, the hands or the feet alone approximately in 21% of cases. Aberrant Sonic—hedgehog signalling has been suggested to account for features of polydactyly of BBS [11].
3. Truncal Obesity: Obesity was reported in 72% of cases [12]. Defects in leptin action may be responsible for the development of obesity in BBS. Other recent studies suggest that BBS proteins may also be involved in adipogenesis and future studies will need to determine it [13, 14].
4. Hypogonadism: Hypogonadism is more frequent in males than in females. Most males have micropenis at birth with small volume testes, atrophic seminiferous tubules. Hypogonadism in females may not be apparent until puberty, when delay in onset of secondary sexual characters and menarche become evident. Genito urinary malformations such as hypo plastic fallopian tubes, uterus, ovaries have been reported. But several affected females have given birth [9].
5. Renal anomalies: Renal involvement leading to chronic renal failure occurs in 30–60% of patients. Hypertension has been noted in 50–66% of cases. Structural and functional abnormalities were noted [15].

Minor Criteria

Learning disabilities, Speech delay, Developmental delay, Behavioural abnormalities, Eye abnormalities, Brachydactyly/Syndactyly, Ataxia, Mild hypertonia, Diabetes

mellitus, Orodonal abnormalities, Cardio Vascular Anomaly, Anosmia etc. [9].

Diagnosis: Presence of four major or three major and two minor criteria are required for diagnosing the BBS.

BBS Proteins in Ciliary Function

Cilia are microtubule based appendages that extend from the basal bodies of cells and are either motile or immotile [16]. Primary cilia are immotile and are present on almost on all human cell types [17]. Photoreceptors, olfactory cilia and cilia on epithelial cells in Kidney that act as mechanosensors are all primary cilia [18]. Seven of the BBS proteins (BBS 1, 2, 4, 5, 7, 8 & 9), mediate function of primary cilia [19]. The defects in neuronal signaling are likely components of many BBS phenotypes including obesity, hypogonadism and cognitive defects.

Molecular Genetics

So far, 14 genes causing BBS, their location and function are known. Sequence analysis is available for all 14 known BBS-related genes. Mutations range for missense and nonsense to insertions, deletions and splice site-disruptions [20].

Approximately, 20% of persons with BBS do not have identifiable mutation in any of the 14 BBS genes. It indicates that additional BBS genes and their mutation have yet to be identified [21].

Establishing the Diagnosis

The diagnosis of BBS relies on clinical findings, on family history. Molecular genetic testing using clinically available tests can be used to confirm diagnosis. Carrier testing for at risk relatives requires prior identification of the disease causing mutations in the family.

Prenatal Diagnosis

Prenatal diagnosis for pregnant women at increased risk for BBS is possible by analysis of DNA extracted from foetal cells, obtained by amniocentesis at 15–18 weeks of gestation or by chorionic villi sampling at 10–12 weeks of gestation. Both the disease causing alleles of an affected family member must be identified before prenatal testing can be performed. Pre implantation genetic diagnosis may be available for families in which the disease causing mutation have been identified [22].

Management of BBS

The management of BBS is supportive therapy, based on the extent of the disease in a diagnosed individual. The disease severity can be evaluated by (1) ophthalmic assessment for visual acuity, field defects or refractive errors, fundoscopic photographs should be preserved for comparison. (2) Examination of genitalia in both the sexes. In affected females image the ovaries, fallopian tubes, uterus and vagina by pelvic ultrasonography. (3) Obesity can be evaluated by calculating BMI. (4) Renal function tests and renal ultrasound examination for anomalies. (5) Cardiac evaluation can be done by ECG and ECHO cardiographic examination. (6) Neurological examination for sensory and motor skills. (7) Hearing evaluation. (8) Endocrinological evaluation for thyroid function, glucose tolerance and pituitary function for infertility.

Therapy is based on the findings, it may be conservative or surgical. No therapy exists for visual loss. Obesity management is by introducing life style modification, educating the patient regarding diet and exercise. Speech therapy for delayed speech and learning disabilities. Surgical correction for gonadal problems. At puberty, gonadotropin and sex hormone levels should be monitored to determine if hormone replacement therapy is required. It is important to offer contraceptive advice to all affected females rather than assume likely infertility. Renal failure patients can be treated by haemodialysis or peritoneal dialysis, renal transplantation can be offered for chronic renal failure. Genetic counseling is advised for affected individuals [23].

Conclusion

To conclude renal profile indicating ESRD in young subjects may be one of the diagnostic feature of BBS. In cases of fertile females if BBS has been diagnosed, detailed family history must be taken. If possible and needed pre-natal genetic testing must be done to identify whether the foetus will be a carrier or will get affected. As the management is supportive, better supportive care can be given to the individuals by prior diagnosis.

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