

Bardet Biedl syndrome: A rare genetic disorder

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Abstract

Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder. Clinical presentation of this rare condition may affect locomotive, neurological, cardio-vascular, endocrine and metabolic systems. Other noticeable features of the disorder are vision loss, obesity, polydactyly, kidney failure, hypogonadism and slow mental processing. We present the case of a Bardet-Biedl syndrome that appeared in the emergency room with seizures due to hypocalcaemia. Because of unusual body habitus and involvement of multiple body organ systems, a genetic diagnosis was sought. A web-based search was prompted as a resource to figure out rare clinical syndrome like BBS, and its further management particularly genetic counselling.

Keywords: Polydactyly, chronic kidneys disease (CKD), vision loss, Bardet Biedl Syndrome

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Introduction

Bardet-Biedl syndrome is an autosomal recessive genetic disorder. The frequency of its clinical presentation ranges from 1/140000 to 1/160000 among the population. Multi-organ involvement may include vision loss, obesity, polydactyly, kidney failure, hypogonadism, slow mental processing, delayed speech, learning disability, motor disability (ataxia, poor coordination), anosmia, cardiac problems (LVH, dilated cardiomyopathies, IVS hypertrophy), Hirschsprung disease, auditory problems, diabetes mellitus, hypertension and hyperlipidaemia.^{1,2}

Beals PL et al has devised a criteria for the diagnosis of BBS.³ Among the primary features of the disease, any four of the following are a requisite: (a) polydactyly (b) retinal dystrophy (c) learning difficulties (d) hypogonadism in males (e) renal structural abnormalities and (f) obesity. Alternatively two secondary features to three primary features are required for its diagnosis: (a) Speech defects/delay (b) diabetes mellitus (c) nephrogenic diabetes insipidus (d) developmental delay (e) brachydactyly/syndactyly (f) ataxia/poor coordination/imbalance (g) mild spasticity (especially lower limbs) (h) strabismus/cataracts/astigmatism (i) dental crowding/

missing teeth/short roots/high arched palate (j) left ventricular hypertrophy or congenital heart disease and (k) hepatic fibrosis.

The objective of publishing this case is to convey that a rare genetic disorder like BBS can present itself in the emergency room. Unusual body habitus and multi-organ involvement mandate a search for a genetic diagnosis. Evidence of a pattern of genetic inheritance can help in genetic counselling as the disease can manifest and significantly impact the next generations, especially in the case of an autosomal recessive disorder like BBS. Web-based searches can provide information for the diagnosis of such rare and infamous syndromes.

Case Report

An informed consent was taken from the patient and his family for publication of this case report. A 30-year old male presented in the Nishtar hospital emergency department in September 2018 with a history of three seizure episodes over the last one day. Seizures were tonic-clonic in nature, lasting for 2-3 minutes, with loss of consciousness and frothing from mouth and without faecal or urinary incontinence. Fits were not preceded by aura, fever, headache, altered level of consciousness, head injury or any ear discharge. He had no previous history of meningitis or stroke, tobacco, alcohol or drug abuse. Patient lost his vision about 12 years ago. He was also a known chronic kidney disease (CKD) case for last 2 months but without any renal replacement therapy. Clinical evaluation revealed hypercalcaemia as the cause of seizure which was treated successfully. Polydactyly in hands and feet and loss of vision for the last 12 years raised the suspicion of a syndromic presence, as shown in figure 1. Further evaluation showed presence of truncal obesity (BMI 26.8), webbed neck, malar hypoplasia, gynaecomastia, high arched palate without dental anomalies, cardiomyopathy, bilateral retinitis pigmentosa, under-pneumatisation of mastoid air cells, normal range for FSH and LH hormones, small kidneys etc. Family history showed remarkable consanguinity. Paternal cousins had polydactyly, blindness and had off-spring with similar medical condition. The patient went to school only for a few months but couldn't cope with the studies due to poor vision and learning difficulties.

Our cases met the diagnostic criteria for Bardet-Biedl syndrome with presence of blindness, CKD, polydactyly,

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Figure: Polydactyly in hand & feet of Bardet-Biedl Syndrome.

obesity, learning difficulties etc. Presence of consanguinity and a similar case within the family further supported the existence of this syndrome in the patient. No genetic testing was performed due to limited resources.

Discussion

Bardet-Biedl Syndrome (BBS) has autosomal recessive pattern of inheritance. If both parents are carriers of the causative gene, chances of their offspring inheriting having a syndromic

presentation is 25%.⁴ Consanguinity can contribute significantly towards prevalence of autosomal recessive disorder and its further descent into future generations.⁵ Different identified defective genes called BBSomes are associated with BBS like BBS1, BBS2, ARL6/BBS3, BBS4, BBS5, BBS7, TTC8/BBS8, BBS10, TRIM32/BBS11, BBS12, CCDC28B, CEP290, TMEM67, MKS1, MKKS.⁶ Gene product of the above mentioned genes is called BBS-protein and is located in the basal part of the human cell and in cilia. It plays a role in intra-flagellar transport (IFT) as found in the experimental study in roundworm model (*C. Elegans*).⁷ Thus ciliopathy is the reason for the disease and involves multi-organ systems in BBS (Pleiotropy). The frequency of organ involvement may vary from case to case. Obesity, renal involvement, polydactyly, learning difficulties, blindness are the most noticeable features of the disease and present with a frequency of 70%, 100%, 45%, 62% and 93.8% respectively.⁸⁻¹⁰ It is however worth mentioning that the diagnosis of BBS is mainly based on clinical presentation. Genetic confirmation is needed when clinical presentation is atypical or unclear.

Diagnosis of the syndrome is often delayed as the development of clinical features like renal disease, blindness and learning disabilities etc are gradual at the onset, along with a lack of awareness among clinicians about this infamous genetic disorder. The element of consanguinity manifests in 39% of the reported cases. Certain parts of Canada and Kuwait harbour the highest prevalence of BBS among the population, although both localities are very different in cultural background. True prevalence of BBS due to consanguinity in a zone like Pakistan is unknown.¹¹ However genetic education of the autosomal disorder can produce a favourable outcome in a detected family.¹²

Conclusion

Bardet Biedl syndrome is a genetic disorder and mostly remains under diagnosed. Whenever a clinician comes across a patient with polydactyly and obesity and/or blindness and/or renal failure, screening for BBS is recommended. In time, genetic counselling can prevent the further propagation of the disease in the next generation.

Limitations

Diagnosis of Bardet Biedl syndrome is based on clinical criteria as mentioned by Beales PL et al. However, we did not confirm the genetic diagnosis due to limited resources.

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