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REVIEW ARTICLE

Prenatal Diagnosis of Bardet-Biedl Syndrome: A Case Study and Review of Literature

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Abstract Bardet-Biedl syndrome (BBS) is a rare autosomal recessive disease with a prevalence rate of 1 in 125,000–170,000. BBS can occur as a result of mutation in one of the 19 known genes of the BBS gene complex. The syndrome is mostly diagnosed post-natally based on the structural and functional manifestations of the disease in childhood like short stature, obesity, polydactyly or syndactyly, retinal dystrophy, structural renal abnormalities, neurodevelopment delays, mental retardation, diabetes mellitus. We present a case of Bardet-Biedl syndrome diagnosed prenatally at 18 weeks gestation based on prenatal ultrasound findings of post axial polydactyly with bilateral hyperechogenic kidneys. Clinical suspicion based on ultrasound findings was supplemented amniocentesis and clinical exome sequencing. This showed a pathogenic variant in homozygous state in the *MKKS* gene, consistent with Bardet-Biedl syndrome type 6. Unless BBS has been suspected antenatally, diagnosis of BBS is usually made in late childhood or early adulthood adding to the psychological, emotional and financial burden on the family. With advances in prenatal ultrasound techniques and tremendous improvement in genetic diagnosis of suspicious findings on ultrasonography, diagnosis of rare genetic disorders like BBS is now possible as early as the 18–20 weeks scan. This can aid in appropriate counseling of the family and timely intervention in children born with this condition.

Keywords Bardet-biedl syndrome · Prenatal ultrasound · Polydactyly · Echogenic kidney · Amniocentesis · Clinical exome sequencing

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Introduction

Bardet-Biedl syndrome (BBS) is a rare, genetically determined, serious autosomal recessive disease with a prevalence rate of 1 in 125,000–170,000. BBS can occur due to a mutation in one of the 19 known genes also known as the BBS gene complex. These genes are important for the structure and functioning of cilia present on the eukaryotic cells [1]. On one hand where the motile cilia are responsible for the movement of fluids in the body, non motile cilia are responsible for transmitting sensory signals to the photoreceptors of the retina, cells of smell (olfactory cells) or hearing.

BBS is a disease of the non motile cilia and manifestations of the disease are generally in childhood and present with structural and functional problems of short stature, obesity, polydactyly or syndactyly, retinal dystrophy, structural renal abnormalities, neurodevelopment delays, mental retardation, and diabetes milletus [2].

Although individual phenotypes are highly variable, clinical features may include ataxia, learning disabilities, hypertension, anosmia, auditory deficiencies, hepatic fibrosis, and Hirschsprung disease. All these manifestations greatly increase the morbidity, putting tremendous stress on the developmental, social and financial aspects associated with the upbringing of the affected child.

Till 2012, less than 15 cases had been reported from India and that too in postnatal life [3]. With the advances in ultrasound, genetics and Fetal Medicine it is now possible to detect such rare and serious syndromes antenatally to aid in counseling and timely intervention in such children born with disabilities.

We present a case of Bardet-Biedl syndrome diagnosed prenatally in a woman with a consanguineous marriage who presented to a tertiary care centre in North India in the second trimester with suspicion of bilateral echogenic kidneys and elucidate the detailed workup of a fetus with bilateral echogenic kidneys on prenatal ultrasound and the role of detailed genetic workup and clinical exome sequencing in such cases.

Case Report

Mrs X, 42 years old, G3 P2 L2 presented to our centre for a first trimester screening at 12 weeks of gestation. On eliciting detailed history, it was found that the first child had mild neurodevelopmental delay with a history of surgery for removal of a small sixth digit tag (postaxial polydactyly). The child had also undergone tendinoplasty for Congenital Talipes Equinovarus (CTEV) and had an optical correction for myopia. On physical examination, the child appeared obese and used special orthopaedic shoes for gait correction. He went to a normal school but had below average performance. Imaging of the first child had revealed normal MRI of the brain with mild hydronephrosis of both kidneys.

Her second pregnancy was uneventful and a healthy girl child was delivered by cesarean section 6 years ago. The indication for cesarean was previous delivery by cesarean section.

A clinical exome was ordered for the first child in view of the phenotypic features. First trimester screening was done of the present pregnancy which raised a suspicion of polydactyly and the patient was called back for a review at 16–17 weeks.

On a detailed anomaly scan at 17 weeks, fetal growth was normal. There was evidence of post axial polydactyly in all the extremities (Fig. 1). The kidneys appeared hyperechogenic as compared to the adjacent liver and spleen parenchyma. The size was normal. Renal parenchyma was homogenously hyperechogenic with no corticomedullary differentiation. There was no evidence of any cystic lesion at the time of the scan (Fig. 2a, b). No significant pelvicalyceal dilatation was observed. The urinary bladder appeared normal in shape and size. Amniotic fluid volume was normal. Bilateral CTEV was noted. There were no other obvious structural defects. Clinical exome sequencing of the first child (index case) revealed a homozygous likely pathogenic variant, c.549del p.(Leu183Phefs*14), in the *MKKS* gene.

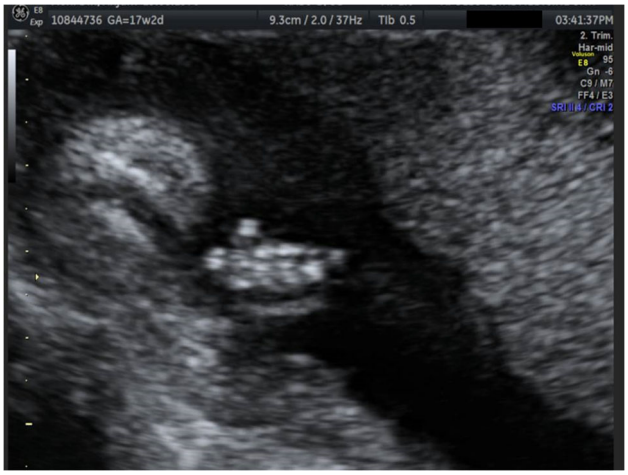

Fig. 1 High resolution ultrasound scan image using 3.5 MHz convex probe showing post-axial polydactyly in a 17 week POG fetus

After detailed counseling and informed consent an amniocentesis was done and the sample was sent for genetic testing (clinical exome sequencing). Prenatal testing for the known familial variant was requested. The known familial likely pathogenic variant was identified in homozygous state in the *MKKS* gene. The obtained result was consistent with the genetic diagnosis of Bardet-Biedl syndrome type 6. After a detailed genetic counseling, the parents decided to discontinue the pregnancy.

Discussion

Bardet-Biedl syndrome for many years was considered a part of Laurence-Moon-Bardet-Bield syndrome but is now considered a separate entity. In 80 percent of the cases it is carried in an autosomal recessive manner. The prevalence of the disease as aforementioned is 1 in 125,000–1 in 160,000. The incidence is more in countries where consanguineous marriages are common like in Bedouin tribes of the Negev region of Israel and in families of European ancestry in the island portion of Newfoundland where the incidence is as high as 1 in 13,500 and 1 in 17,500 respectively [4].

Post natal diagnosis of Bardet-Biedl syndrome is based on symptomatology of the affected child. The rapid development of genetic testing over the last decade has led to the discovery of changes that take places in one of the 19 genes in clinically diagnosed patients with BBS, encompassing mis-sense, nonsense and frame-shift mutations [5].

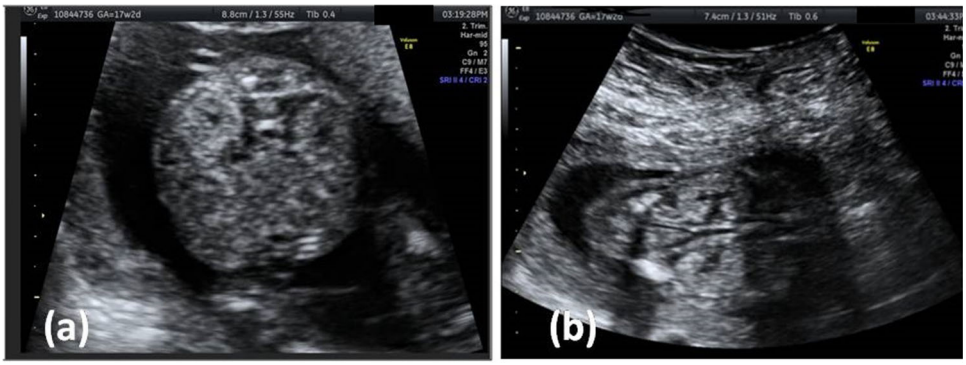

Fig. 2 High resolution ultrasound scan images using 3.5 MHz convex probe showing, **a** Axial and **b** Coronal view of echogenic kidney at 17 weeks of getation

Genetic Basis of the Disease

The last decade has seen the discovery of 16 genes which are responsible for causation of 80% of BBS. BBS1 and BBS10 gene mutations are responsible for the majority of pathognomic gene mutations accounting for 23.3% and 20% respectively [6].

Also, over the past decade there has been rising evidence that genes involved in BBS and other ciliopathies exhibit some overlap [7]. It has been seen that BBS2, BBS4, BBS6 gene mutations are found in patients suffering from Meckel syndrome [8]. Similarly, MKKS gene mutation is seen in patients with BBS and Joubert's syndrome [9]. Such a condition was seen in our patient who was identified to have a homozygous state in the MKKS gene. The obtained result was consistent with the genetic diagnosis of BBS type 6.

Clinical Course

Unless BBS has been suspected antenatally, the diagnosis of BBS is usually made in late childhood or early adulthood.

The most common symptom prompting investigation in a child is the gradual onset of night blindness followed by photophobia and loss of colour and central vision which is because of the loss of rod photoreceptors followed by cone photoreceptors. Symptoms usually develop in the first decade of life and most patients become visually handicapped by second or the third decade [10], although less severe forms of the disease presentation are also known. These changes can be recognized by electroretinography. Significant changes are rarely seen before the age of five years [11].

The other major clinical finding that aids to the diagnosis of BBS postnatally is the development of obesity in children. This is present in 70–86% of the patients with BBS [12, 13]. At birth these children tend to have normal weight but most of them develop obesity within the first year of life [14].

Owing to the early onset of obesity, type 2 diabetes mellitus is prevalent in these patients and is found in association with other features of metabolic syndrome.

Renal abnormalities are invariably present in patients with BBS and significantly contribute to the morbidity and mortality [15]. It is classically present in the form of cystic tubular disease [14].

The neurodevelopmental delays associated with BBS pose a great challenge in the upbringing of the affected children. These children generally have global developmental delays [11]. They have outbursts of frustration and many choose to have a fixed routine associated with obsessive compulsive disorders and lack of social dominance [16]. Many are also seen to be affected with autism spectrum disorder [16].

As cited above, although individual phenotypes are highly variable, other clinical features may include ataxia, learning disabilities, hypertension, anosmia, auditory deficiencies, hepatic fibrosis, and Hirschsprung disease.

Prenatal Diagnosis of BBS

Renal hyperechogenicity is diagnosed after 17 weeks gestation when the kidneys appear more echogenic as compared to the liver and spleen [17]. With advances in prenatal ultrasound techniques and the previous decade showing tremendous improvement in genetic diagnosis of suspicious findings on ultrasonography, the diagnosis of such rare genetic disorders like BBS is now possible as early as in early second trimester with high index of suspicion as early as in the first trimester scan.

The most common findings on ultrasonography is the presence of hyperechogenic kidneys along with polydactyly. Autosomal recessive Polycystic Kidney disease (ARPKD) and Autosomal Dominant Polycystic Kidney disease (ADPKD) are the most common differential diagnosis when dealing with hyperechogenic kidneys in an anomaly scan, but whenever there is a history of consanguineous marriages and previous births affected with a disabled child as in the present case, the diagnosis of BBS

should be kept in mind. The other important differential diagnosis of hyperechogenic kidneys and associated syndromes is given in Table 1 [17–19].

The clues in our case that helped us come to such an early diagnosis at 16–18 weeks of gestation was a history of a consanguineous marriage, an affected disabled child and a strong suspicion of polydactyly in the first trimester ultrasound. This helped us in proper counseling and timely genetic testing of the index case. The early anomaly scan revealed polydactyly along with hyperechoic kidneys that clinched the diagnosis and as the result of the genetic evaluation of the index case was available at this time, timely invasive testing could be done before 20 weeks and a definitive diagnosis of BBS could be reached.

Clinical Use of Exome Sequencing

DNA was extracted directly by amniocentesis after taking informed written consent.

Clinical exome sequencing previously performed in the index patient of the family revealed a homozygous likely pathogenic variant, c.549del p.(Leu183Phefs*14), in the MKKS gene. Targeted sequencing was performed on both DNA strands of the relevant MKKS region. The reference sequence was: MKKS: NM_170784.2

The known familial likely pathogenic variant was identified in homozygous state in the MKKS gene. The obtained result was consistent with the genetic diagnosis of Bardet-Biedl syndrome type 6 (Table 2).

Variant Interpretation

*MKKS, c.549del p.(Leu183Phefs*14)* The known MKKS variant c.549del p.(Leu183Phefs*14) creates a shift in the reading frame starting at codon 183. The new reading frame ends in a stop codon 13 positions downstream. This variant has been confirmed by Sanger sequencing. It is classified as likely pathogenic (class 2) according to the recommendations of ACMG. Pathogenic variants in the

Table 1 Differential diagnosis of hyperechogenic kidneys and associated syndromes [18]

Syndrome	Transmission	Frequency	Findings
Trisomy 13	Chromosomal aberration	1/1000	Omphalocoele, genitourinary abnormalities, polydactyly, club foot (congenital talipes equinovarus), congenital heart defects
Trisomy 18	Chromosomal aberration	1/5500	Intrauterine growth restriction, hypertonia, micrognathia, horseshoe kidney, flexed fingers, congenital heart defects
ADPKD	Autosomal dominant	1/1000	Enlarged hyperechogenic kidneys, increased CMD, uncommon associated malformations
ARPKD	Autosomal recessive	1/40,000	Enlarged hyperechogenic kidneys, absence of CMD, oligohydramnios, uncommon associated malformations
Meckel-Gruber AR	Autosomal recessive	rare	Medullary cystic dysplasia, severe oligohydramnios, CNS anomaly, polydactyly
Bardet-Biedl	Autosomal recessive	1/125,000–1/160,000	Enlarged hyperechogenic kidneys (30–100%), absence of CMD, digital anomalies
Beckwith Wiedemann	Imprinting disorder	1/14,000	Macroglossia, macrosomia, omphalocele, hemihyperplasia, renal medullary dysplasia, polyhydramnios
Ivemark II	Autosomal recessive	rare	Asplenia–polysplenia, cystic liver, kidney and pancreas
Tuberous sclerosis Complex	AD/ de novo mutation	1/5800	Angiofibromas, ungual fibromas, cortical tubers, angiolipomas in the kidney, cardiac rhabdomyomas
Zellweger syndrome	Autosomal recessive	1/50,000–100,000	AR Intrauterine growth restriction, muscular hypotonia, increased nuchal translucency, abnormal head shape, micrognathia, hydrocephalus, ventriculomegaly, agenesis, or hypoplasia of the corpus callosum
17q12 deletion syndrome	Autosomal dominant	unknown	Deletion of the 17q12 chromosome results in structural or functional abnormalities in the kidneys and the urethra, type 5 diabetes and neuro-developmental disorders. Prenatally cystic kidneys are a common feature. Less common features include esophageal atresia, eye abnormalities, cleft palate, heart defects and sex reversal [19]

ARPKD Autosomal Recessive Polycystic Kidney disease; *ADPKD* Autosomal Dominant Polycystic Kidney disease; *CMD* Cortico-medullary differentiation; *AR* Autosomal recessive; *CNS* Central Nervous System; *AD* Autosomal Dominant

Table 2 Result summary of genetic test

Gene	Variant coordinates	Zygosity	In-silico parameters*	Type and classification***
MKKS	Chr20(GRCh37):g.10393614 del	Homozygous	Poly Phen: N/A	Frameshift
	NM_018848.3:c.549del		Align-GVGD: N/A	Likely pathogenic
	p.(Leu183Phefs*14)		SIFT: N/A	(class 2)
	Exon 3		Mutation Taster: N/A	

Variant description based on Alamut Batch (latest database available)

*Align GVD: C0: least likely to interfere with function, C65: most likely to interfere with function, splice prediction tools: SSF, Max Ent, HSF

***based on ACMG recommendations

MKKS gene are causative for Bardet-Biedl syndrome type 6, an autosomal recessive disorder.

Conclusion

Bardet-Biedl is a rare autosomal recessive disorder. Diagnosis of BBS is usually made in late childhood or early adulthood with psychological, emotional and financial consequences on the family. With advances in prenatal ultrasound techniques and tremendous improvement in genetic workup and diagnosis like use of clinical exome sequencing for suspicious findings on ultrasonography like bilateral echogenic kidneys, diagnosis of rare genetic disorders like BBS is now possible as early as the 18–20 weeks scan. This can aid in the proper counseling and timely intervention in such children born with disabilities.

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Compliance with Ethical Standards

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Ethics Approval Signed informed consent for publication of a case report was obtained from the patient described in the report. IRB/Ethics Committee ruled that approval was not required for this study.

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