World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Check for updates

Understanding Bardet-Biedl Syndrome: Unveiling the Complexities of this Rare Genetic Disorder and its Systematic Review to Identify its Various Variants with Genetic Analysis.

Furqan Ul Haq [1,*], Asad Riaz [2], Izhar Ullah [3], Nawab Ali [4], Itizaz Khan [5], Jibran Ikram [6], Asad Ur Rahman [7], Irfan Ullah [8], Khizer Hamza [9], Kamran Ahmad [10], Zeeshan Khan [11], Shahzad Zafar [12], Fahad Rahman [13] and Aisha Maqbool [14]

[1] *Radiation Oncology Department, Shifa International Hospital, Limited, Pakistan.*
[2] *General Surgery Department, Ayub Teaching Hospital, Abbottabad, Pakistan.*
[3] *General Medicine Department, Khyber Teaching Hospital Peshawar, Pakistan.*
[4] *Anesthesia Department, Lady Reading Hospital Peshawar, Pakistan.*
[5] *Cardiology Department, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom*
[6] *Department of Medicine, Rehman Medical Institute, Peshawar, Pakistan.*
[7] *Department of Medicine, Hayatabad Medical Complex, Peshawar, Pakistan.*
[8] *Department of Medicine, Hayatabad Medical Complex, Peshawar, Pakistan.*
[9] *Pathology Department, Gajju Khan Medical College, Sawabi, Pakistan.*
[10] *Department of Medicine, Hayatabad Medical Complex, Peshawar, Pakistan.*
[11] *Department of Medicine, Saidu General Teaching Hospital, Swat. Pakistan.*
[12] *Basic Speciality Training Department, Saint LUKE Hospital Dublin Ireland.*
[13] *General Medicine Department, Khyber Teaching Hospital Peshawar, Pakistan.*
[14] *Department of Medicine, Niazi Medical College Sargodha Punjab Pakistan.*

World Journal of Advanced Research and Reviews, 2024, 22(01), 088–096

Publication history: Received on 05 February 2024; revised on 27 March 2024; accepted on 30 March 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.22.1.1073

Abstract

Background: There are a variety of clinical features associated with Bardet-Biedl Syndrome (BBS), a rare genetic disorder affecting several organ systems. First identified in the early 20th century, BBS has since been the subject of extensive research to understand its underlying genetics, clinical presentation, and management. This article provides a comprehensive background on BBS, highlighting its clinical manifestations, genetic basis, and current research efforts.

Introduction: BBS is a multisystem, genetic, autosomal recessive heterogeneous cilia structural and functional disorder (occurs when one gene influences two or more seemingly unrelated phenotypic traits) characterized by structural and functional abnormalities of organ and tissues with diverse embryonic derivation. It was first described by Laurence and Moon in 1866. It is caused by loss of proteins coding by the BBS gene. It is characterized by retinal degeneration, post-axial polydactyly, obesity, cognitive deficit, hypogonadism, and cognitive dysfunction. Associated features are diabetes mellitus, hypertension, congenital heart disease, speech defects, dental anomalies, and hepatic fibrosis. In order to diagnose the BBS, molecular genetic tests, such as whole-exome sequencing or whole-genome sequencing is considered useful.

Case: A 16 year old girl presented to us in the general medicine ward through the Emergency department with the complaints of dyspnea for six months, fever for three days, and dysuria for three days. Her fever was associated with rigors and chills. On further questioning, her urine was reported to have a bad smell. Past medical history was positive for otitis media and falls. She needed walking support as she was unable to see at night time. On physical examination a

* Corresponding author: Furqan Ul Haq

young lady was laying in the supine position. She was pale, obese and had high respiratory rate. There was no lymphadenopathy. Extra digits were noted in her upper and lower limbs. Rest of the physical examination was normal. The patient was started on 2 liters of oxygen and blood samples were taken for laboratory investigations.

Conclusion: As this was diagnosed on time, so it helped both the family and physcians to check on her weight, respiratory functions, skeletal abnormalities, sexual development, visual acquity, cardiac functioning, hepatic functioning and hematologic stability such as hemoglobin. Being a very rare disease a therefore this disease awareness is necessary among physicians to diagnose the disease early and treat the complications of the disease so that the complications do not progress to the stage where it is irreversible. Early detection of renal problem, visual problems, obesity, and learning disabilities is necessary to be treated on time by involving multidisciplinary approaches.

Keywords: Bardet Beidel syndrome; Obesity; Vision problems; Rare syndromes; Pediatrics syndromes; Autosomal recessive syndromes; Polydactyly

1. Introduction

Bardet beidel Syndrome (BBS) is a rare autosomal recessive disease commonly found in consanguineous marriages. The disease typically appears in the first decade of life with vision problems as the first symptom. It has been studied to have multi systemic ciliopathies (Cilium formation defects), with prevalence of 1:25,000, with different ethnicities the prevalence ratio is variable. It is identified that 22 genes have been studied and found to be associated with BBS, those genes are these genes are responsible to be transcribed and forms proteins such as BBSome protein, basal body interacting protein, chaperonin complex protein and several others. Among North Americans and Europeans, the incidence of live births varies between 1:140,000 and 1:160,000. On the other hand, the rate is much greater in Kuwait and Newfoundland, where it is estimated to occur at 1:13500 and 1:17500, respectively. In addition to retinal degeneration and postaxial polydactyly, the disease also causes obesity, mental retardation, hypogonadism, and renal malformations. [1].

Associated features of the disease include diabetes mellitus, hypertension, congenital heart disease, facial dysmorphism, speech defects, dental anomalies, and hepatic fibrosis. Additionally, it is common to observe nystagmus and a narrowing of the peripheral visual fields. The fundus exhibits significant changes including constricted arterioles, a pale appearance of the optic disc, and alterations in peripheral pigmentation such as pigment atrophy and the presence of white deposits. In the early stages, degenerative changes are apparent in the maculae of affected individuals, resulting in a persistent decline in their central vision. Consequently, these individuals become legally blind by the age of 30. Electroretinography confirms the presence of diffuse photoreceptor disease, which helps distinguish BBS from retinitis pigmentosa, a condition unrelated to any systemic disease.

Molecular genetic testing plays a crucial role in the diagnosis of BBS by identifying mutations or pathogenic variants in BBS-related genes. Various techniques, including targeted sequencing, whole-exome sequencing (WES), and whole-genome sequencing (WGS), can be utilized to pinpoint the specific genetic abnormalities associated with BBS and confirm the diagnosis. It has been observed that women are more commonly affected than men in over half of all reported cases. Additionally, up to 90% of affected patients exhibit functional and morphological abnormalities. Renal abnormalities, which often lead to significant morbidity, are prevalent and have been identified as the primary cause of mortality based on autopsy records. Here we will discuss first our case report and then we will add its genetic systematic review analysis, the different types of BBS, the associated proteins defects and associated genes have been mentioned in the later part of the article.

2. Case presentation

A 16 years old girl presented in the general medicine ward through the Emergency department with the complaints of dyspnea for six months, fever for three days, and dysuria for three days. The dyspnea was gradual in onset and aggravated with mild exertion and relieved with rest. There was no associated cough, chest pain, and orthopnea or paroxysmal nocturnal dyspnea. She had sudden onset, high grade, continuous fever which was associated with chills and rigors. She had dysuria for three days and her urine was reported to have a bad smell. She had a past medical history of recurrent otitis media and recurrent falls. She needed a walking support ad she was unable to see at night time. Her family history was not significant. Her vital signs were normal except high respiratory rate. Upon physical examination, she was pale, obese, and there was no lymphadenopathy. She had deep-set eye sockets, a small or sloping forehead, and a broad nasal bridge (Figure 1). She had brachydactyly (Figure 2) and had extra digits in her upper and lower limbs (Figure 3 and 4).

The patient was started on 2 liters of oxygen.

Laboratory investigations showed anemia and thrombocytopenia, have been explained in (Table 1) in details with normal ranges as well. X-ray of the hands showed short and curved fingers, changes in the shape of the bones in the wrists and an extra 6th finger in right hand (Figure 3). Ultrasound of the abdomen and pelvis showed multiple cysts in kidneys and ovaries and enlarged spleen, these findings are mentioned for the patient in (table 2) have been compare to other BBS ultra sonographic findings in patients. She was not able to afford genetic testing so she did not underwent any sort of confirmatory genetic testing.

She was diagnosed with BBS based upon her clinical features, laboratory investigations and imaging findings. She was treated with fluids, iron replacement, antibiotic and multivitamins, these treatment at hospital and at home have been mentioned in details with doses and route of administration as well, along with future precautionary measures to be taken in the (table 3). Further follow up of the patient was scheduled to see the any complications and its timely management.

Figure 1 Typical Facial features of Bardet Biedl Syndrome having deep-set eye socket, a small or sloping forehead, and a broad nasal bridge

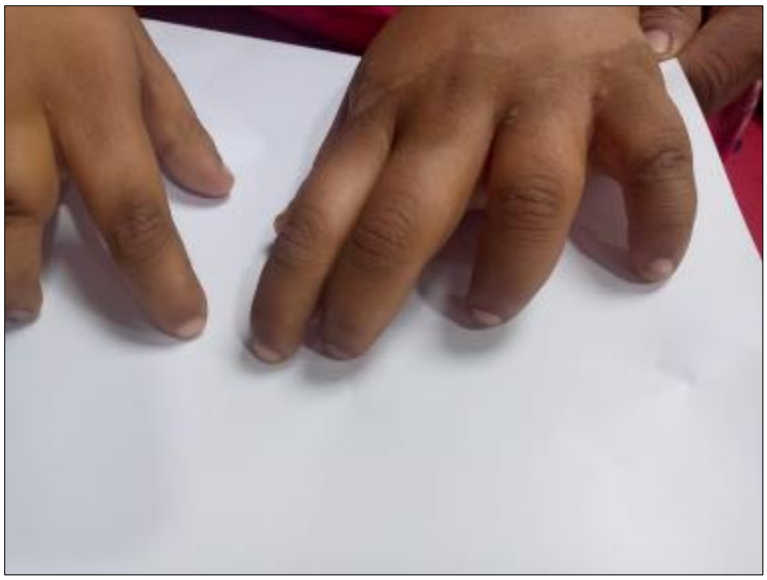

Figure 2 Hands showing Brachydactyly (unusually short fingers) and Nail abnormalities (discolored nails)

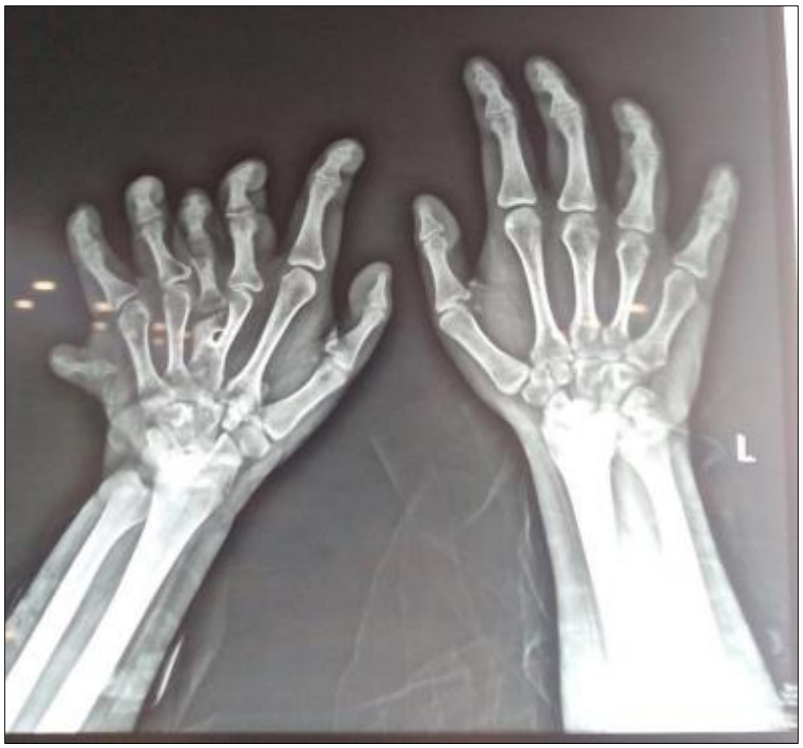

Figure 3 Hand x-rays showing curving of the fingers, shortening of the fingers, and changes in the shape of the bones in the wrist and an extra 6th and 7th finger in right hand

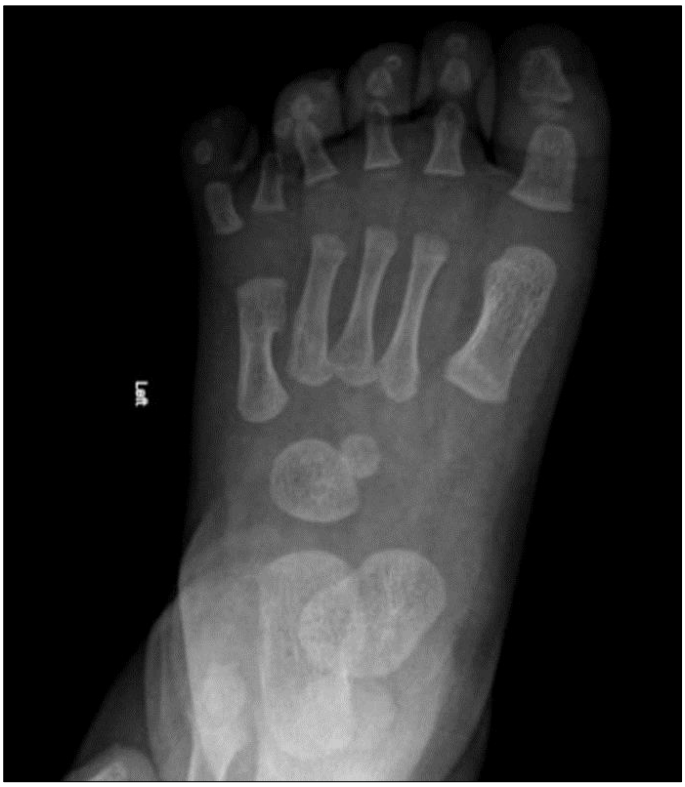

Figure 4 X ray left foot in PA view, shows an extra digit at the meta traso phalangeal joint towards on the lateral side

Table 1 Base line hematologic investigations

Name of investigation	Results	Normal Range	Unit
Hemoglobin	4.5	M=14-18 F= 11.7-15.7	mg/dl
WBC	5	4.0-10.0	$x10^3/dL$
Neutrophils	70%	40-70%	$x10^3/dL$
Lymphocytes	21%	20-25%	$x10^3/dL$
Monocytes	5%	2-10%	$x10^3/dL$
Eosinophils	2%	1-2%	$x10^3/dL$
Platelets Count	110	150-400	$x10^6/L$
Sodium	137	136-149	mmol/L
Potassium	3.7	3.8-5.2	mmol/L
Chloride	98	98-107	mmol/L
Random Blood Sugar	110	80-140	mg/dl
Blood Urea	27	10-50	mg/dl
Alkaline Phosphatase	79	40-129	mg/dl
Serum Calcium (Total)	9.3	8.8-12.0	mg/dl
Total Bilirubin	0.9	0.1-1	mg/dl
PTH-Intact		15-65	pg/ml
Alpha Fetoprotein		0-6	IU/ml
Physical examination of stool			
Color	yellowish	Yellowish	NIL
Reaction	acidic	Acidic	NIL
Consistency	solid	Solid	NIL
Blood	nil	NIL	/hpf
Mucus	nil	NIL	/hpf
Microscopic examination of stool			
Ova	nil	NIL	/hpf
Cyst	nil	NIL	/hpf
Pus Cells	nil	NIL	/hpf
RBCs	nil	NIL	/hpf

Abbreviations: WBCs: white blood cells; RBCs red blood cells; PTH: parathyroid harmone; mg/dL: milligram per decilitre; mmol/L: millimole per litre; pg/ml: picogram per millilitre; IU: international units; hpf: high power field

Table 2 Here are some common ultrasound findings in the abdomen and pelvis associated with Bordet-Biedl Syndrome (BBS) versus our patient, presented in tabulated form

1	Organ/system	Ultra sound findings in BBS	Ultrasound findings in our patients
2	Kidneys	Renal cysts, renal hyper echogenicity, and renal malformations.	Renal cysts found in the left kidney (less than 1 centimetre).
3	Liver	Fatty liver and hepatomegaly	Nil
4	Pancreas	Pancreatic cysts and pancreatic calcifications	Nil
5	Spleen	Splenomegaly and splenic cysts	Mild splenomegaly
6	Adrenal Glands	Adrenal gland hyperplasia or cysts	Nil
7	Gastrointestinal	Intestinal malrotation and malformations of the gastrointestinal tract	Nil
8	Genitourinary Tract	Uterine or testicular abnormalities and urinary tract malformations	Nil
9	Pelvic Structures	Ovarian cysts and uterine fibroids	Multiple ovarian cysts bilaterally (less than 1cm)

Table 3 Treatment given to the patient

Serial No.	Name of a drug	Route of administration	Dosage	Duration
1	Ceftriaxone	IV	1g BD	5 days
2	Venofer	IV	1g OD	3 days
3	Normal saline 0.9%	IV	500ml BD	3 days
4	Vitamin D analogues	Per Oral	2000 IU	3 days a week
Home Treatment				
1	Surbex Z	Per Oral	1 tablet	continue
2	Qalsium D	Per oral	1 Tablet	continue
3	Continuous monitoring of Liver function, visual acuity, renal functions, cardiac function and skeletal profile has been advised			

IV: intravenous; BD: two times a day; OD: once a day

3. Literature Review of its various variants

BBS s an autosomal recessive disorder in which there is multi systemic ciliopathies (Cilium formation defects), with prevalence of 1:25,000, with different ethnicities the prevalence ratio is variable. It has been identified that 22 genes have been studied and found to be associated with BBS, those genes are responsible to be transcribed and forms proteins such as BBSome protein, basal body interacting protein, chaperonin complex protein and several others have been explained in the (Table 4). The ciliary structural and functional diaghram, the associated class of proteins in cilia, and the associated syndromes when there is defect in those proteins have been explained in (Figure 5).

Table 4 Representing the proteins and their associated encoding class of genes, so far 7 proteins of cilia have been explained in this article

S.N	Protein	Genes association found to cause BBS
1	BBSome protein	BBS1, BBS2, BBS4, BBS5, BBS7, BBS8 (TTC8), BBS9 (PTHB1), BBS17 (LZTFL1), and BBS18 (BBIP1)
2	basal body interacting protein	BSS13 (MKS1), BBS14 (CEP290; TMEM67), BBS15 (WDPCP), and BBS16 (SDCCAG8)
3	chaperonin complex protein	BBS6 (MKKS), BBS10, and BBS12
4	E3 ubiquitin ligase	BBS11 (TRIM32)
5	GTPase protein complex	BBS3 (ARL6), BBS19 (IFT27), and BBS20 (IFT172)
6	primary cilia function	BBS21 (C8ORF37)
7	centrosome and ciliary proteins	BBS22 (CEP19)

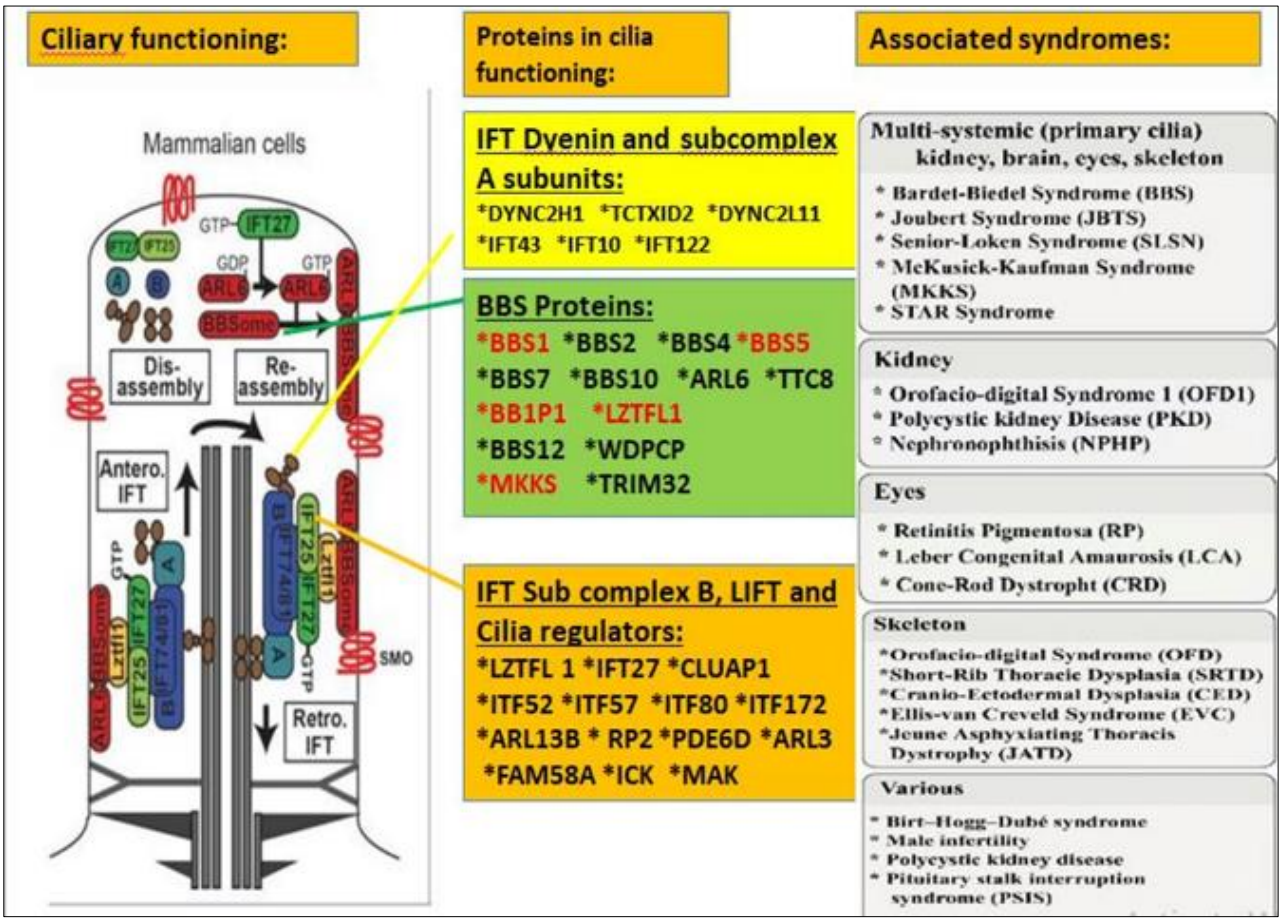

Figure 5 These are the genes associated with BBS, the figure is showing antero grade and retrograde movement across cilia, these are the different proteins with the respective encoding genes as well, the red tagged genes are studied and found to be in patients found in Pakistan. The associated syndromes have also been mentioned in different systems or organs of the body associated with ciliary dysfunction

4. Discussion

Bardet-Biedl syndrome (BBS) is an uncommon genetic condition that impacts several organ systems. It falls under the category of ciliopathies, a group of disorders distinguished by abnormalities in the primary cilium, a slender, hair-like structure present on the surface of most human cells. BBS exhibits several clinical features, including retinal dystrophy, obesity, post-axial polydactyly, renal dysfunction, learning difficulties, and hypogonadism. Additional minor characteristics can assist in both diagnosis and management of the condition. Clinical criteria are used to diagnose BBS, and genetic testing can confirm the diagnosis.[3] In a documented case, a newborn with heterotaxy, duodenal atresia, and complex cardiac malformation was found to have BBS through whole-genome sequencing. This emphasizes the importance of considering BBS as a potential diagnosis in infants presenting with multiple congenital anomalies.[4] The syndrome's global prevalence is estimated to range from one in 100,000 to one in 160,000 individuals. The genetic underpinnings of BBS are complex, with 21 distinct genes identified thus far that play a role in the formation and function of cilia.[5] Cilia are hair-like structures on cell surfaces crucial for cellular signaling and communication. Due to the clinical and genetic heterogeneity of BBS, diagnosis can pose challenges. A comprehensive evaluation strategy, encompassing a detailed medical history, physical examination, and genetic testing, is necessary to determine the genetic cause of BBS in a patient. In some instances, the genetic cause may remain unidentified, while in other cases, it may involve a variant of uncertain significance. A dysfunction of cilia is related to the underlying pathophysiology of BBS, which leads to abnormalities across multiple body systems[6]. A person with BBS may experience different symptoms depending on the severity and distribution of these abnormalities. For example, retinal dystrophy can cause vision loss, while renal abnormalities can lead to renal failure. Obesity is also a common feature of BBS and can contribute to a variety of health problems, including cardiovascular disease and diabetes. The diagnosis of BBS can be challenging, and a comprehensive evaluation is required to establish the diagnosis. Genetic testing is considered the gold standard for the diagnosis of BBS, as it can identify pathogenic variants in one of the 21 genes known to cause the disorder[7]. However, clinical evaluation, including a thorough medical history, physical examination, and specific diagnostic tests, may also be useful in establishing a diagnosis of BBS[8]. Our patient presented with symptoms of fever, dyspnea, dysuria and recurrent otitis media which has not been reported in previous literature about Bardet Biedl syndrome[9]. She had recurrent symptoms of ear infections and difficulty with balancing aswell[10]. Along with that, she was having dyspnea with exertion which could be due to anemia (Hb 4.5) and dysuria aswell[11]. Currently, there is no cure for BBS, and management of the condition is mainly focused on treating individual symptoms[12]. For instance, treatment of retinal dystrophy involves regular eye examinations and use of low vision aids such as magnifying glasses, telescopes, and electronic devices[13]. Weight management and dietary interventions are important to prevent obesity and related complications such as diabetes, hypertension, and cardiovascular disease. Polydactyly can be surgically corrected, and renal dysfunction can be treated with medications and sometimes requires kidney transplantation[14].

5. Conclusion

As Bardet Beidl syndrome(BBS) is a rare hereditary condition, BBS has the potential to impact multiple bodily systems. Consequently, it is crucial for healthcare professionals to possess knowledge about this disorder, enabling early diagnosis and timely management of associated complications. Early detection of BBS-related problems such as renal issues, visual impairments, obesity, and learning disabilities can help to prevent the complications from worsening to a point where they become untreatable. In our case, a BBS patient has been presented with recurrent otitis media and urethritis as well, therefore physicians need to be aware about this complication as well and further studies need to be done to find out any correlation for it.

As such, raising awareness of this condition is critical for providing the best possible care for those affected by BBS. It is also important for physicians to be aware of the range of treatments available for this condition, as well as any lifestyle modifications that may help to improve the patient's quality of life. By increasing knowledge of this rare disorder, physicians can ensure that those affected are able to access the best possible care and lead a full, healthy life.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

No intervention was done by the researcher and the team has taken inform consent from the patient and her family to publish this knowledge for educational purpose.

Author Contributions

All authors contributed equally.

Grant Information

The authors declared that no grants were Involved in supporting this work.

References

[1] Suspitsin EN, Imyanitov EN. Bardet-Biedl Syndrome. Mol Syndromol. 2016 May;7(2):62-71. doi: 10.1159/000445491. Epub 2016 Apr 15. PMID: 27385962; PMCID: PMC4906432.

[2] Arora E, Fuks A, Meyer J, Chervenak J. Prenatal diagnosis of Bardet Biedl Syndrome: A case report. Radiol Case Rep. 2022 Nov 14;18(1):326-330. doi: 10.1016/j.radcr.2022.10.040. PMID: 36406960; PMCID: PMC9668600.

[3] Forsythe E, Beales PL. Bardet-Biedl syndrome. Eur J Hum Genet. 2013 Jan;21(1):8-13. doi: 10.1038/ejhg.2012.115. Epub 2012 Jun 20. PMID: 22713813; PMCID: PMC3522196.

[4] Forsyth R, Gunay-Aygun M. Bardet-Biedl Syndrome Overview. 2003 Jul 14 [updated 2023 Mar 23]. In: Adam MP, Mirza GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023. PMID: 20301537.

[5] Kops SA, Kylat RI, Bhatia S, Seckeler MD, Barber BJ, Bader MY. Genetic Characterization of a Model Ciliopathy: Bardet-Biedl Syndrome. J Pediatr Genet. 2021 Jun;10(2):126-130. doi: 10.1055/s-0040-1708844. Epub 2020 Mar 31. PMID: 33996183; PMCID: PMC8110344.

[6] Ece Solmaz A, Onay H, Atik T, Aykut A, Cerrah Gunes M, Ozalp Yuregir O, Bas VN, Hazan F, Kirbiyik O, Ozkinay F. Targeted multi-gene panel testing for the diagnosis of Bardet Biedl syndrome: Identification of nine novel mutations across BBS1, BBS2, BBS4, BBS7, BBS9, BBS10 genes. Eur J Med Genet. 2015 Dec;58(12):689-94. doi: 10.1016/j.ejmg.2015.10.011. Epub 2015 Oct 27. PMID: 26518167.

[7] Xia Y, Li X, Chen X, Lu C, Yu X. Inferring Retinal Degeneration-Related Genes Based on Xgboost. Front Mol Biosci. 2022 Feb 11; 9:843150. doi: 10.3389/fmolb.2022.843150. PMID: 35223997; PMCID: PMC8880610.

[8] Stoetzel C, Muller J, Laurier V, et al. Identification of a novel BBS gene (BBS12) highlights the major role of a vertebrate-specific branch of chaperonin-related proteins in Bardet-Biedl syndrome. Am J Hum Genet. 2007;80(1):1-11. doi:10.1086/510256

[9] Zaghloul NA, Katsanis N. Mechanistic insights into Bardet-Biedl syndrome, a model ciliopathy. J Clin Invest. 2009;119(3):428-437. doi:10.1172/JCI37041

[10] Moore SJ, Green JS, Fan Y, et al. Clinical and genetic epidemiology of Bardet-Biedl syndrome in Newfoundland: a 22-year prospective, population-based, cohort study. Am J Med Genet A. 2005;132A(4):352-360. doi:10.1002/ajmg.a.30400

[11] Beales PL, Warner AM, Hitman GA, Thakker R, Flinter FA. Bardet-Biedl syndrome: a molecular and phenotypic study of 18 families. J Med Genet. 1997;34(2):92-98. doi:10.1136/jmg.34.2.92

[12] Khan SA, Muhammad N, Khan MA, et al. Genetics of human Bardet-Biedl syndrome, an update. Clin Genet. 2016;90(1):3-15. doi:10.1111/cge.12706

[13] Hjortshøj TD, Grønskov K, Brøndum-Nielsen K, Rosenberg T. A novel founder BBS1 mutation explains a unique high prevalence of Bardet-Biedl syndrome in the Faroe Islands. Br J Ophthalmol. 2009;93(3):409-413. doi:10.1136/bjo.2008.141208

[14] Marion V, Stoetzel C, Schlicht D, et al. Transient ciliogenesis involving Bardet-Biedl syndrome proteins is a fundamental characteristic of adipogenic differentiation. Proc Natl Acad Sci USA. 2009;106(6):1820-1825. doi:10.1073/pnas.0806097106