Case Report

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Bardet–Biedl syndrome with unique manifestations of congenital giant nevi and refractory anemia: a case report from Palestine

Mohammad Milhem, MD[a,*], Daleen Shehadeh, MD[a], Yasmeen Abu Nawa, MD[a], Roa Arman, MD[a], Lara Masri, MD[a], Zeena Salman, MD[b], Mohammad Najajreh, MD[a,b]

Introduction and importance: Bardet–Biedl syndrome (BBS) is a rare autosomal recessive disorder impacting multiple organs. Characterized by renal dysfunction, retinal dystrophy, obesity, polydactyly, intellectual disability, and hypogonadism, it lacks targeted treatment. Diagnosis relies on clinical criteria, and management emphasizes early detection, complication screening, and genetic counselling.

Case presentation: A 4-year-old boy, born to first-cousin parents, presented with refractory iron-deficiency anaemia (IDA) and recurrent respiratory infections. Prenatal ultrasound revealed renal and limb anomalies. Physical examination showed dysmorphic features, polydactyly, and a giant-congenital naevus. Genetic testing revealed a homozygous MKKS variant. Despite oral iron, severe IDA persisted. Intravenous iron therapy yielded significant improvement.

Clinical discussion: BBS, an autosomal recessive ciliopathy, involves various genes. In this case, the MKKS gene variant contributed to the syndrome. The incidence of BBS in the Arab population is discussed, emphasizing its rarity and varied clinical presentations. Incidence in the Arab population, including Palestine, is 1 in 13 500. Diagnostic criteria, encompassing major and minor features, highlight BBS complexity. Renal anomalies, visual disturbances, and cutaneous manifestations are common. Multidisciplinary care addresses systemic involvement with emerging treatments like setmelanotide.

Conclusion: This case underscores BBS's rarity and complexity, featuring unique aspects like giant nevi and refractory IDA. Comprehensive management addresses renal, visual, cardiac, and neurologic aspects. Genetic counselling, prenatal testing, and preimplantation genetic diagnosis prevent transmission. Limitations include lacking local epidemiological data and prior studies in Palestine. This case contributes insights, stressing multidisciplinary management and prompting further research in underexplored populations.

Keywords: bardet–biedl syndrome, congenital nevi, obesity, polydactyly, retinitis pigmentosa

Introduction

Bardet–Biedl syndrome (BBS) is a rare autosomal recessive inherited disorder that affects both sexes equally. BBS was first discovered in the 1920s and named after the researchers who first described the syndrome: Bardet and Biedl in 1920 and 1922, respectively[1,2].

BBS affects multiple organs and systems and is characterized by renal dysfunction, progressive cone-rod dystrophy, central obesity, postaxial polydactyly, intellectual disability, and hypogonadism[3–5]. Geographic distribution is variable, with incidence ranging from 1:160 000 in Europe to 1:13 500 in some Arab populations[6].

The mutations most associated with this syndrome are in the BBS1 and BBS10 genes, leading to disruption of cell-signal transduction pathways due to hindrance of the primary cilia-sensory organelle function that regulates it. Thus, the diversity of clinical presentation results from the ciliary dysfunction involving multiple systems, such as the retina, nervous and genitourinary systems, liver, and heart[7].

HIGHLIGHTS

- Bardet–Biedl syndrome (BBS) is a rare genetic disorder; its diagnosis is based on clinical criteria and molecular-genetic testing.
- The first reported case of BBS in Palestine. The incidence of BBS in the Arab population, including Palestine, is estimated to be about 1 in 13 500.
- A case of BBS with unique presentation not included in the diagnostic criteria involving congenital giant nevi and refractory iron-deficiency anaemia.
- The dramatic improvement of BBS cases with refractory iron-deficiency anaemia to IV Iron therapy.

[a]Faculty of Medicine, Palestine Polytechnic University, Hebron and [b]Department of The Huda Al Masri Pediatric Cancer, Beit Jala Hospital, Beit Jala, Palestine

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*Corresponding author. Address: Palestine Polytechnic University located in Hebron, West Bank, Palestine. Tel.: +970 259 444 0318. E-mail: ben_milhem@outlook.com (M. I. Milhem).

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Diagnosis of BBS is achieved by the modified clinical criteria proposed by Beales and colleagues clinical diagnosis is defined by the presence of four major criteria or three major and at least two minor criteria. Major criteria include cone-rod dystrophy, polydactyly, cognitive impairment, renal dysfunction, obesity, and hypogonadism. Minor criteria include hepatic and cardiac arrest, diabetes insipidus, dental anomalies, gait ataxia, brachydactyly and/or syndactyly, and developmental and speech delay[1].

No targeted treatment currently exists for BBS. The focus of management is on early diagnosis, screening for complications, and genetic counselling. Additionally, strict control of blood-pressure levels, lipid profile, and body mass are critical to the management of BBS.

The novelty of this case lies in its contribution to the understanding of BBS in Palestine, the atypical clinical features observed, the genetic insights provided, and the implications for the management of associated complications. These aspects collectively make the case a valuable addition to the literature on BBS, warranting publication to disseminate knowledge and guide future research and clinical practice.

Case presentation

Our patient is a 4-year-old boy diagnosed with Bardet Beidl syndrome. He was referred to our paediatric haematology clinic due to refractory anaemia. He also had a history of recurrent respiratory tract infections requiring paediatric intensive care unit admission. The patient is the third child of parents of Arab origin, who are first cousins.

He was born full-term via caesarean section delivery with a birth weight of 3.5 kg.

Antenatally, at 20 weeks gestation, a detailed foetal ultrasound revealed both kidneys enlarged and echogenic, with early features of dysplasia. The same foetal ultrasound demonstrated polydactyly in all four limbs. Follow-up renal ultrasound after birth reported that both kidneys were enlarged in size and bright in echogenicity, with a loss of corticomedullary differentiation. A follow-up renal ultrasound at the age of three years showed that both kidneys were normal in size, shape, echo structure, and position, with normal cortical thickness and no hydronephrosis.

Family history includes a father with a history of rheumatic disorder and the death of an older male sibling at age 3 years, reportedly due to congenital heart disease.

A physical examination at presentation revealed a giant-congenital naevus with multiple smaller nevi all over the body" Figure 1". Several dysmorphic features were also observed, namely a broad depressed nasal bridge, full cheeks, narrow bi-frontal diameter, thin lips, and low-set, small ears with deformity of the left ear pinna. Examination of the extremities revealed postaxial polydactyly and central polydactyly of the left hand (7 digits), central polydactyly of the right hand (6 digits), postaxial polydactyly of both feet (6 digits each), and abnormal left palmar creases "Figure 2". BMI was 26.3 kg/m^2, which is overweight according to the WHO classification for BMI. Based on these findings, the patient was referred to a multidisciplinary team for evaluation.

Ophthalmological examination revealed esotropia, mild cyclo-refraction-hypermetropia with healthy optic discs, and

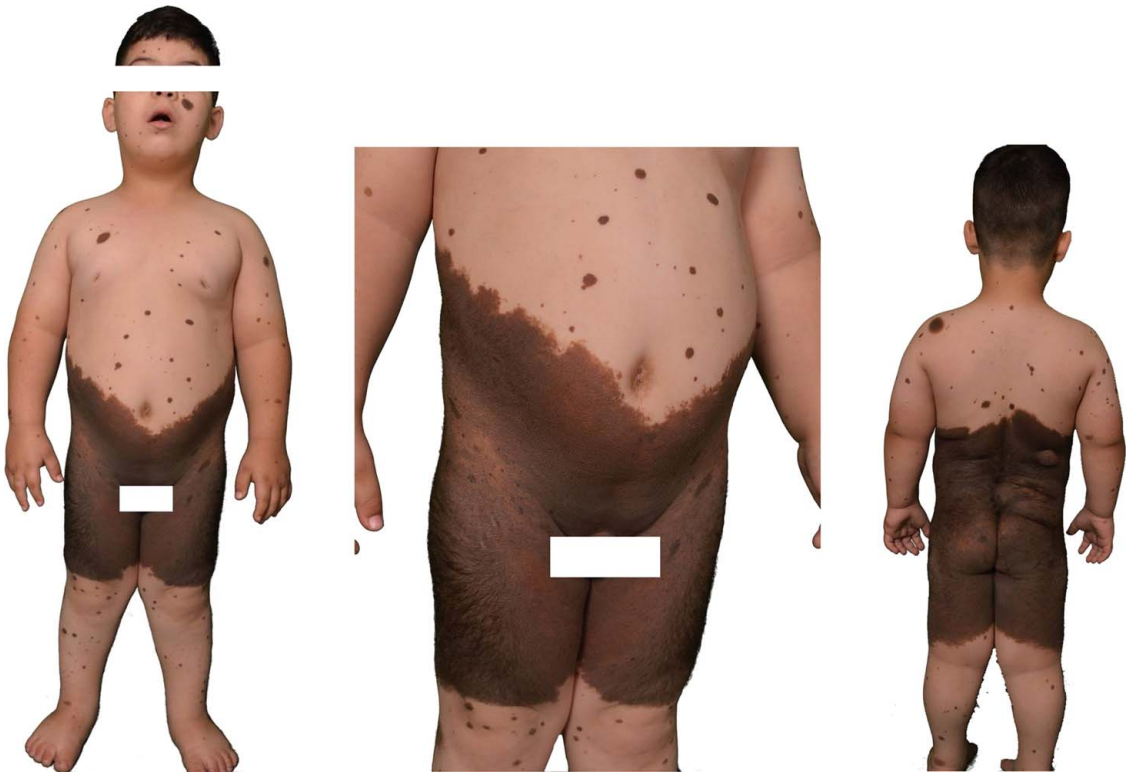

Figure 1. Giant congenital naevus (a large, dark-coloured patch of skin) extending from the mid of the abdomen to both knees with multiple smaller nevi (spots or moles) over a body of a 4-year-old boy with Bardet–Biedl syndrome. The lower body is censored for privacy.

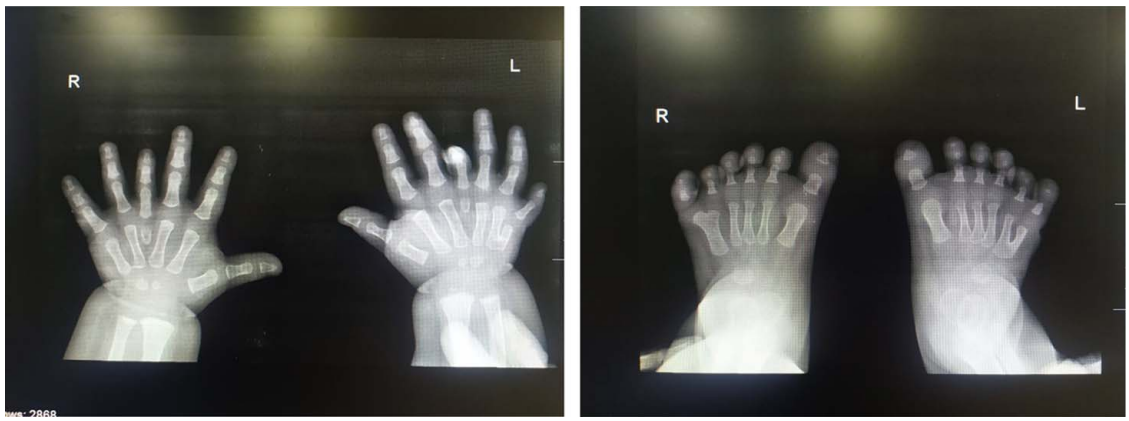

Figure 2. images of X-rays of hands and feet, showing polydactyly of the both hand and both feet. The left hand has two extra digits (central and postaxial) and each foot has one extra digit.

retinal vasculature. Neurologic evaluation revealed language impairment with a limited vocabulary and expressions. Electroencephalography and brain MRI investigations were unremarkable. Laboratory test results were normal.

Exome sequencing was performed and showed that he is homozygous for a variant (chr20: 10393994 T > C; c.169A > G; p.Thr57Ala) in the MMKs gene. Pathogenic variants in this gene cause BBS.

Gene	Variant coordinates	Zygosity	Allele frequency	In-silico parameters	Type and classification***
MMKS	Chr20:10393994 T > C (GRCh37) NM_018848:C. A169G p.Thr57Ala Exon 3	Homozygous	PopFreMax:-In-house*:- gnomAD**:-	SIFT:0 Polyphen:1 REVEL:0.827 GERP: 4.96	Nonsynonymous Pathogenic (Class1)

*Palestinian In-house database, **gnomAD: Genome aggregation Database.
***IAH VARIANT CLASSIFICATION (BASED ON ACMG RECOMMENDATIONS).
Class1—Pathogenic.
Class 2—Likely pathogenic.
Class 3—Variant of uncertain significance (VUS).
Class 4—Likely benign.
Class 5—Benign.

On arrival at our paediatric haematology-oncology clinic, the child was clinically stable, with pallor. Physical examination revealed the aforementioned dysmorphic features associated with a remarkable congenital giant naevus distending from the mid-trunk region to the mid-thigh. He was started on oral iron treatment for more than four months with minimal improvement in the haemoglobin level. His complete blood count was indicative of severe iron-deficiency anaemia, with a haemoglobin level of 8.1 g/dl; mean corpuscular volume of 40.6 fl; mean corpuscular hemoglobin of 10.8 pg per cell, platelet count of 751 10^9/l, reticulocyte count of 1.5% and haemoglobin electrophoresis was normal.

His iron study revealed a serum iron level of 9 ug/dl, ferritin of 3.91 ng/ml, and a total iron binding capacity of 512 mcg/dl. His blood urea nitrogen and creatinine were normal.

We decided to treat him with intravenous iron 100 mg weekly, to which his haemoglobin responded well at 1 month -up, with an increase to 11 and greater than 13 at 3-month follow-up. Serum iron, serum ferritin and reticulocyte count also improved dramatically at 1 month to 45 ug/dl, 15.54 ng/ml and 1.9%, respectively.

Discussion

BBS is a rare autosomal recessive or oligogenic ciliopathy with multiple organs involvement characterized by the cardinal features of postaxial polydactyly, retinitis pigmentosa, kidney defects, obesity, intellectual disability, and behavioural disorders (autism, psychosis). Rapid weight gain is frequently mentioned in early infancy, and beyond age 5, over 90% of patients are obese or overweight. It can be hard to control the weight gain and often leads to metabolic syndrome in adults[8].

BBS is presented as pathogenic homozygous or compound heterozygous variants (a total of 24 ciliopathy-causing genes of BBS, some complex have now been discovered)[9]. BBS1 (11q13.2) and BBS10 (12q21.2) are the most common genes, accounting for roughly 23% and 15% of genotyped BBS patients, respectively[8].

In the reported case, the patient is a homozygous variant child of heterozygous first-cousin parents. He possesses a mutation in the MKKS gene, classified as class 1 (pathogenic) according to the American College of Medical Genetics (ACMG). The MKKS c. A169G p.Thr57Ala is a nonsynonymous variant that creates an amino acid substitution of threonine at position 57 with alanine on chromosome 20.

In the reported case, the patient is a homozygous variant child of heterozygous first-cousin parents. He possesses a mutation in the MKKS gene, classified as class 1 (pathogenic) according to the American College of Medical Genetics (ACMG). The MKKS c. A169G p.Thr57Ala is a nonsynonymous variant that creates an amino acid substitution of threonine at position 57 with alanine on chromosome 20. According to a study published in the Journal of Community Genetics in 2017, the incidence of BBS in the Arab population, including Palestine, is estimated to be around 1 in 13 500. It is important to note that incidence rates can vary depending on different factors such as geography, population size, and genetic predisposition.

According to diagnostic criteria, four primary or three primary and two secondary criteria are sufficient for the diagnosis. Five primary and four secondary features were present in our patient. Therefore meeting the BBS diagnostic criteria[10].

Primary features	Secondary features
Cone-rod dystrophy	Speech delay
Obesity	Developmental delay
Polydactyly	Brachydactyly/syndactyly
Genital anomalies	Ataxia/poor coordination
Learning difficulties	Diabetes mellitus
Renal anomalies	Dental anomalies
	Anosmia/hyposmia
	Deafness
	Congenital heart disease
	Hepatic fibrosis
	Mild spasticity
	Strabismus/cataract/astigmatism

Diagnostic criteria for BBS 1

In patients without polydactyly, visual manifestations are frequently the first sign that can assist with diagnosis; polydactyly and kidney anomalies (hyperechoic or multicystic kidneys) may be prenatal presenting indicators. BBS patients have been shown to have a number of renal abnormalities, including chronic kidney disease, parenchymal cysts, calyceal clubbing, foetal lobulation, renal scarring, unilateral agenesis, dysplastic kidneys, renal calculi, and vesicoureteral reflux[11].

Cutaneous manifestations are frequent in BBS and indicate both systemic effects of BBS on the health of the skin and disturbances in keratinization and keratinocyte function. In the reported case, exome sequencing did not reveal any causative or associated genetic causes for the congenital melanocytic nevi, which arises from a somatic mutation.

In the paediatric age group, the majority of the lesions were located on the upper extremity, and the most common histological subtypes were pigmented and compound variants. In adults, the lesions were chiefly located on the lower extremity, and the most common histological subtype was the desmoplastic variant[12].

Multidisciplinary care with regular follow-up is critical to formulate and coordinate management and therapeutic interventions, including the evaluation and appropriate management of renal disease, hypogonadism, polydactyly, dental abnormalities (dental crowding, hypodontia, malocclusion, enamel hypoplasia), congenital heart disease (valvular stenosis, patent ductus arteriosus), cardiomyopathy, obesity, visual abnormalities (including regular replacement of prescription lenses), paediatric neurology clinic, dermatology, growth and development; also encouragement should be given for a healthy diet (limited in calories and protein) and exercise routines. Setmelanotide, which acts on the melanocortin-4 receptor, is approved for hunger control in genetically confirmed BBS patients. Genital abnormalities and polydactyly may be treated with surgery.

Transmission of the mutated gene from both parents to their offspring can be prevented by prenatal testing and preimplantation genetic diagnosis (PGD). Thus, we recommend genetic counselling and testing for the familial mutation for all the family members before marriage or prior to every pregnancy.

The incidence of anaemia or giant nevi in BBS is not well-established, as these are rare features of a rare syndrome. However, some studies have reported the occurrence of these conditions in BBS patients. For example, one case report described a 16-year-old girl with BBS who had megaloblastic anaemia, which is a type of anaemia caused by vitamin B12 deficiency. A second case report described a 6-year-old boy with BBS who had a giant naevus on his back.

The lack of previous studies on BBS in Palestine made it impossible to make any generalizations, and this was one of the limitations that we faced. Additionally, the lack of local epidemiological information about the syndrome, along with incomplete access to all the relevant medical records or patient information, can limit the scope and accuracy of the report. This can also have an impact on the ability to create a long-term management plan for the patient's condition.

Conclusion

This case report illustrates a 4-year-old child with BBS, a rare genetic disorder characterized by features such as obesity, postaxial polydactyly, cognitive impairment, and visual impairment. BBS affects multiple organs and systems and is diagnosed based on clinical criteria and molecular-genetic testing. In addition to the criteria, our patient has unique presenting features not included in the diagnostic criteria, such as giant-congenital nevi and iron-deficiency anaemia refractory to oral therapy but responsive to intravenous iron. Iron- deficiency anaemia is independent of the syndrome, but further workup is needed to consider malabsorption as part of this disease.

Methods

Medical records of the case were retrospectively reviewed. This work has been reported based on SCARE criteria[13].

Ethical approval

Medical records of the case were retrospectively reviewed.

Consent

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

M.M.: supervision, writing—original draft, review and editing. D.S.: writing—original draft, review and editing, resources. Y.A. N.: writing—original draft, review and editing, data curation,

resources. R.A.: writing—original draft, review and editing, data curation. L.M.: writing—original draft, review and editing, data curation. Z.S.: review and editing. M.N.: review and editing.

Conflicts of interest disclosure

Authors declare that they have No conflicts or source of interests.

Research registration unique identifying number (UIN)

None.

Guarantor

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Availability of data and materials

The datasets used in this report are available from the corresponding author on reasonable request.

Provenance and peer review

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