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BARDET-BIEDL SYNDROME IN TWO SIBLINGS: A RARE ENTITY REVISITED

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ABSTRACT
Bardet-Biedl syndrome (BBS) is a rare autosomal recessive ciliopathy affecting multiple organ systems with significant clinical heterogeneity. We report two siblings, aged 5 and 7 years, born to consanguineous parents, presenting with characteristic BBS features. The 5-year-old female had medically refractory epilepsy, severe obesity (BMI 25 kg/m²), postaxial polydactyly, syndactyly, retinal dystrophy, and night blindness. Her 7-year-old brother exhibited obesity (BMI 24 kg/m²), bilateral postaxial polydactyly, retinal dystrophy, micropenis, and mild hearing loss. Both patients met diagnostic criteria with multiple major criteria. Ophthalmological evaluation confirmed rod-cone dystrophy bilaterally. The female patient's drug-resistant epilepsy represents a rare neurological complication affecting approximately 12% of BBS patients. This case highlights phenotypic variability and emphasizes early recognition for multidisciplinary management. BBS should be considered in differential diagnosis of early-onset obesity with polydactyly and retinal abnormalities, particularly in consanguineous families.

KEYWORDS: Bardet-Biedl syndrome; ciliopathy; polydactyly; retinal dystrophy; epilepsy; consanguinity.

1. INTRODUCTION

Bardet-Biedl syndrome (BBS) is an exceedingly rare autosomal recessive ciliopathy characterized by multisystem involvement and significant phenotypic heterogeneity.[1] First described independently by Georges Bardet and Arthur Biedl in the early 20th century, this genetic disorder affects approximately 1 in 125,000 to 1 in 175,000 individuals in European populations, with higher prevalence rates observed in populations with increased consanguinity rates.[2] Due to its rarity, the syndrome often presents diagnostic and therapeutic challenges, with limited data available regarding optimal management strategies and long-term outcomes in pediatric patients.

The etiology of BBS involves dysfunction of primary cilia, cellular organelles crucial for various signaling pathways including those regulating embryonic development, sensory perception, and metabolic processes.[3] To date, at least 28 distinct genes (BBS1 to BBS28) have been identified as causative for the syndrome, all encoding proteins essential for primary ciliary structure and function.[4] Despite these genetic discoveries, most cases occur with variable penetrance and expressivity, contributing to diagnostic complexity.

The clinical presentation of BBS is characterized by progressive manifestation of multiple organ system involvement. Cardinal features include rod-cone retinal dystrophy leading to progressive visual impairment, early-onset truncal obesity, postaxial polydactyly, hypogonadism, renal abnormalities, and cognitive impairment.[5] The clinical diagnosis is established based on criteria proposed by Beales et al., requiring either four major criteria or three major criteria plus two minor criteria.[6] Neurological manifestations, while recognized, remain poorly characterized, with recent studies identifying epilepsy as an uncommon but significant complication.[7]

Herein, we report two siblings diagnosed with BBS who demonstrate the characteristic phenotypic variability of this syndrome. This case series contributes to the understanding of BBS presentation in pediatric patients, with particular attention to the rare occurrence of medically refractory epilepsy, highlighting the importance of considering rare genetic entities in the differential diagnosis of multisystem disorders in children.

2. CASE PRESENTATION

Two siblings, aged 5 and 7 years respectively, were referred to our pediatric department for evaluation of

multiple congenital anomalies and developmental concerns. Both patients were born to second-degree consanguineous parents following unmonitored pregnancies with term deliveries occurring at home without medical assistance. Family history was notable for consanguinity but negative for similar clinical manifestations.

Case 1: 5-year-old female

The younger sibling presented with a one-month history of medically refractory seizures despite treatment with sodium valproate at 30 mg/kg/day. The parents reported progressive difficulty with night vision beginning at 3.5 years of age, accompanied by severe myopia requiring visual aids. At 4 years of age, the patient developed marked hyperphagia characterized by persistent hunger despite consuming large quantities of food, resulting in rapid weight gain over the subsequent year.

Clinical examination revealed a conscious, well-appearing child in stable condition. Anthropometric measurements demonstrated significant abnormalities with a weight of 28 kg (>+4 SD) and BMI of 25 kg/m², consistent with grade 2 obesity, while height remained within normal parameters. Physical examination revealed right postaxial hexadactyly and bilateral syndactyly between the second and third toes. Cardiovascular, pulmonary, abdominal, and genitourinary examinations were unremarkable.

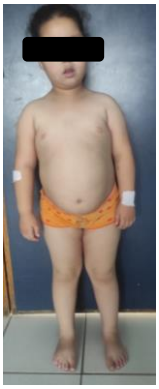

Fig. 1: Central Obesity.

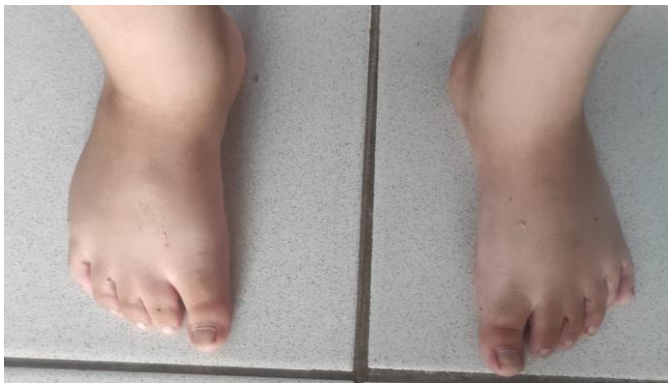

Fig. 2: Post Axial Polydactyly In Right Foot.

Laboratory investigations including complete blood count, comprehensive metabolic panel, renal and hepatic function tests, and glucose profile were within normal limits. Brain magnetic resonance imaging showed no structural abnormalities, however, electroencephalography demonstrated diffuse interictal epileptic discharges with predominance over the right frontal region. Ophthalmological evaluation confirmed bilateral retinal dystrophy consistent with rod-cone dystrophy. Echocardiography and abdominal-renal ultrasonography revealed no abnormalities.

Case 2: 7-year-old male

The elder sibling presented with similar clinical features but without seizure activity. His medical history included hyperphagia since 3 years of age, marked nyctalopia, and surgical removal of right postaxial polydactyly affecting both hand and foot at 5 years of age. Psychomotor development was globally appropriate, though learning difficulties were noted at school.

Physical examination revealed stable condition with weight of 36 kg (>+4 SD) and BMI of 24 kg/m² indicating obesity, while height remained normal. Examination findings included left postaxial polydactyly, bilateral syndactyly between second and third toes, and micropenis. Routine laboratory investigations were within normal limits. Ophthalmological assessment demonstrated bilateral retinal dystrophy, and ENT evaluation revealed mild left-sided sensorineural hearing loss. Echocardiography and abdominal-renal ultrasonography were normal.

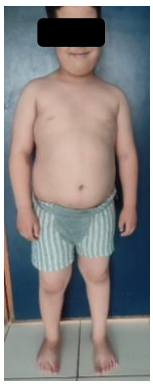

Fig. 1: Central Obesity.

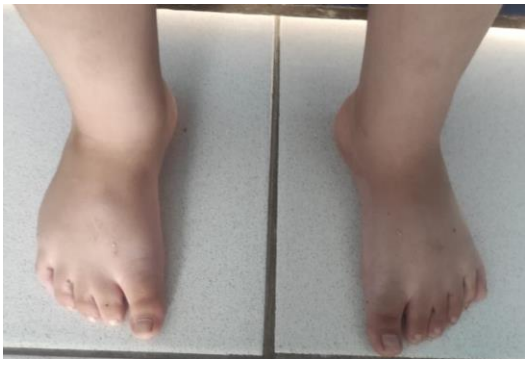

Fig. 2: Post Axial Polydactyly In Right Foot.

Both patients met the diagnostic criteria for BBS according to Beales et al.[6] The female patient satisfied four major criteria (retinal dystrophy, obesity, polydactyly, and cognitive impairment manifesting as epilepsy), while the male patient met five major criteria (retinal dystrophy, obesity, polydactyly, hypogonadism, and cognitive impairment).

3. DISCUSSION

Bardet-Biedl syndrome is characterized histologically and functionally by ciliary dysfunction affecting multiple organ systems.[8] As demonstrated in our cases, the syndrome presents with a constellation of clinical features that typically emerge progressively during the first decade of life. Both patients exhibited the characteristic early-onset obesity, polydactyly, and retinal dystrophy that define this rare ciliopathy.

The progressive retinal dystrophy observed in both patients represents the most debilitating feature of BBS. This rod-cone dystrophy initially manifests as night blindness, as reported in both our patients, followed by progressive peripheral visual field defects and eventual central vision impairment.[9] Unfortunately, this dystrophy remains incurable and typically progresses to legal blindness within the first two decades of life, emphasizing the importance of early visual rehabilitation services.

Early-onset obesity, present in both siblings, typically appears during the second year of life and results from ciliary dysfunction affecting hypothalamic appetite regulation and adipocyte development.[10] The genes responsible for BBS play crucial roles in primary ciliary function during adipocyte maturation. Defective primary cilia lead to altered leptin signaling and premature adipocyte differentiation, promoting excessive fat accumulation that tends to worsen with age.[11]

The extremity abnormalities observed in both patients, including postaxial polydactyly and syndactyly, are consistent with reported prevalence of limb involvement in approximately 70% of BBS cases.[12] These malformations often serve as early diagnostic clues, particularly when present at birth, though the complete syndrome typically becomes apparent only as other features develop over time.

Genitourinary involvement, as demonstrated by micropenis in the male patient, reflects the hypogonadism commonly observed in BBS. This typically affects males more frequently than females, with manifestations including cryptorchidism, micropenis, and hypospadias.[13] In our male patient, the micropenis represents a significant diagnostic criterion supporting the BBS diagnosis.

The occurrence of medically refractory epilepsy in our female patient represents a rare but increasingly recognized complication of BBS. Recent analysis of the international CRIBBS registry revealed that epilepsy affects approximately 12.4% of BBS patients, significantly higher than the general pediatric population.[7] The pathophysiological mechanisms underlying epileptogenesis in BBS remain unclear, though proposed mechanisms include altered neuronal migration, ciliary dysfunction affecting neuronal signaling, and metabolic disturbances secondary to hypothalamic involvement.[14]

The drug-resistant nature of epilepsy in our patient, despite appropriate polytherapy with sodium valproate, underscores the complexity of neurological manifestations in ciliopathies. This highlights the need for specialized neurological management and consideration of alternative therapeutic approaches in BBS patients with seizure disorders.

Cognitive impairment, present in both patients though manifesting differently, affects approximately 50% of BBS patients.[15] The learning difficulties observed in both siblings likely result from ciliary dysfunction affecting neuronal development and synaptic function, though the relationship between cognitive impairment and seizure activity in the female patient requires further evaluation.

Management of BBS requires a comprehensive multidisciplinary approach involving pediatricians, ophthalmologists, endocrinologists, neurologists, and genetic counselors. Key components include early nutritional intervention to prevent obesity-related complications, regular ophthalmological monitoring, and individualized educational support for cognitive and learning difficulties.[16] For patients with epilepsy, specialized neurological evaluation and individualized antiepileptic therapy are essential.

The absence of renal abnormalities in both our patients, while fortunate, does not preclude the BBS diagnosis, as renal involvement occurs in approximately 50% of cases.[17] Annual monitoring of renal function remains important given the potential for progressive chronic kidney disease that can contribute to early mortality in BBS patients.

This case series illustrates the importance of recognizing BBS in pediatric patients presenting with the characteristic constellation of findings, particularly in the setting of consanguinity. Early diagnosis facilitates appropriate multidisciplinary management and genetic counseling, though the progressive nature of key manifestations, particularly visual deterioration, underscores the need for continued research into therapeutic interventions.

4. CONCLUSION

In this context, our case adds valuable insights into the presentation and management of Bardet-Biedl syndrome in pediatric patients, particularly highlighting the

occurrence of medically refractory epilepsy as a rare but significant complication. This report emphasizes the critical role of multidisciplinary evaluation in achieving accurate diagnosis and implementing appropriate management strategies. Bardet-Biedl syndrome, although rare, should be considered in the differential diagnosis of early-onset obesity associated with polydactyly and retinal abnormalities, especially in consanguineous families. Prompt diagnosis and comprehensive multidisciplinary management are essential for optimizing outcomes, though the prognosis for vision remains guarded.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that no generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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