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Image of Interest

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Bardet-Biedl Syndrome

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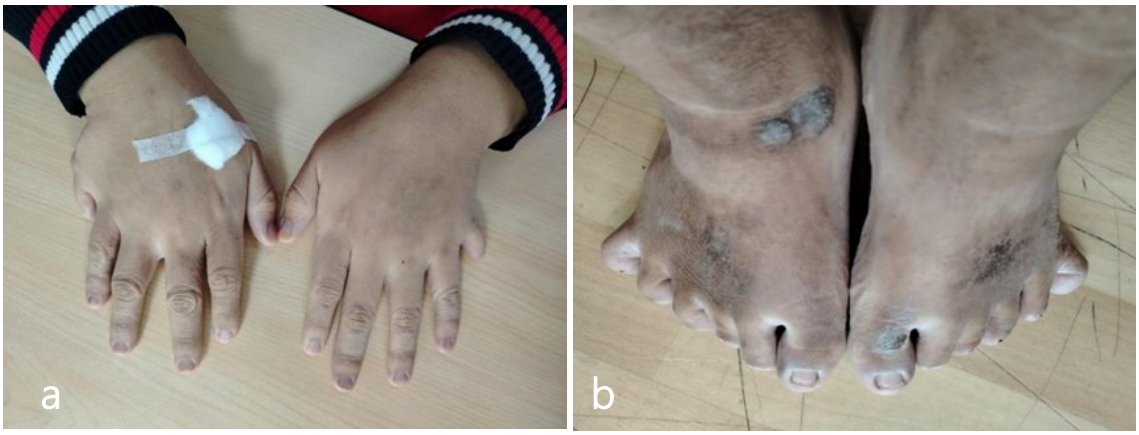

A 29-year-old obese Malay man from the neighbouring state was admitted with complains of high fever, malaise, non-productive cough and dyspnoea on exertion for the past three days. He has a past medical history of chronic kidney disease, hypertension, type 2 diabetes mellitus and bronchial asthma. On examination, he was febrile (39.5^{o} Celsius), alert and oriented, moderate intellectual disability, polydactyly on all four limbs (**Figure 1**), micrognathia and on auscultation of the chest, bi-basal coarse lung crepitations were appreciated. Chest X-ray showed sub-segmental consolidation on left upper lobe and right lower lobe, and he was admitted for treatment of pneumonia.

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Answer: Bardet-Biedl Syndrome (BBS).

BBS is a rare multi-systemic inherited disease which has an autosomal recessive pattern of inheritance. Although traditionally it is believed to be inherited in the above manner, minority of cases reported had tri-allelic mode of inheritance (three mutations in the BBS gene are mandatory before the manifestations of the disease are apparent clinically).[1] Its prevalence is just below 1:100,000 in Europe and Northern America,[1] while it is more common in some Bedouin communities (Middle East) where it can be found in the frequency of 1:13,500.[2]

BBS is an immotile ciliopathy which gives a wide variety of clinical manifestations such as rode-cone dystrophy (often initially presents with night blindness progressing to peripheral vision loss and finally central vision also becomes compromised,[3] polydactyly, central obesity, hypogonadism, genitourinary abnormalities, kidney diseases, neurological abnormalities (epilepsy, psychiatric abnormalities), anosmia, hyposmia, oro-dental abnormalities, gastrointestinal and metabolic abnormalities.[1]

Traditionally, these clinical manifestations are further divided into major criteria and minor criteria for making a clinical diagnosis of BBS (**Table I**).[4-6] Beales *et al.* devised a modified diagnostic criterion which suggests that either four major criteria or three major criteria and two minor criteria would be needed to make a clinical diagnosis of BBS.[4] Suspicion for BBS often starts during prenatal scanning as it often presents with polydactyly, genitourinary abnormalities and renal abnormalities. Central obesity tends to develop in the first year of life, followed by rod-cone dystrophy in the school-age and features of hypogonadism become more noticeable much later in adolescence.[1] Micropenis and/or small volume testes can be a feature in male patients whereas in females it mostly manifests as genital anatomic abnormalities such as absent uretheral/genital orifice, hypoplastic uterus and fallopian tubes.[7]

Recent advances in molecular technology in the past few decades have made it feasible to identify 26 genes which are associated with BBS and are useful in assessing the prognosis and in genetic counselling. Among the most prevalent BBS genes are BBS 1, BBS 2, BBS4, BBS 6, BBS 10 and BBS12 genes.[8] After the identification of BBS related genes, the Clinical Consensus Statement executive group consisting of European healthcare professionals from various specialties have published a new diagnostic criterion in 2024 which includes genetic test results amongst the criteria. Please refer to **Table II** for the diagnostic criteria proposed by Clinical Consensus Statement executive group.[9]

BBS patients have a median survival of 63 years old. The major causes of mortality and morbidity are chronic kidney disease and cardiovascular disease (mainly secondary to the metabolic syndrome).[5,10] Despite recent advancements in molecular technology, no single definitive therapy is currently available for this condition. Management of this genetic disease involves a multidisciplinary approach. Regular surveillance and assessments are necessary from various sub-specialty physicians and health care professionals as required.[1,8,9]

Annual assessment of weight, blood pressure, renal, thyroid and liver function tests, glucose and lipid profile, ophthalmology and endocrinology review are required. Renal ultrasound, DNA for molecular diagnostics, development and educational assessments, hearing evaluation and review by nephrologists, geneticists, clinical psychologists form a fundamental part of the management too. Oral glucose tolerance test and input from speech therapists, cardiologists, orthodontists and mental health professionals are also recommended if required.[1]

Table I: Diagnostic features and their prevalence.[4-6]

Primary features	Prevalence	Secondary features	Prevalence
Rod-cone dystrophy	93%	Speech delay	54-81%
Polydactyly	63-81%	Developmental delay	50-91%
Obesity	72-92%	Diabetes Mellitus	6-48%
Genital anomalies	59-98%	Dental Anomalies	51%
Renal Anomalies	53%	Congenital heart disease	7%
Learning difficulties	61%	Brachydactyly/syndactyly	46-100%/8-95%
		Ataxia/Poor coordination	40-86%
		Anosmia/hyposmia	60%

Age	Clinical Criteria	BBS diagnosis requirements
In Utero	**Primary** • Polydactyly • hyperechogenic kidneys **Secondary** • Hydrometrocolpos • Situs inversus	**Moderate level of confidence:** **Affected sibling BBS gene + ve** At least 1 primary criteria OR 2 primary + 1 secondary criteria BBS gene testing highly recommended **High level of confidence:** Foetus genetic testing + ve + at least 1 primary criteria
0-16 years old	**Primary** • Polydactyly • Early obesity • Early onset retinal dystrophy • Kidney anomalies/dysfunction **Secondary** • Hydrometrocolpos • Micropenis • Neurodevelopmental disability • Anosmia/hyposmia	**Moderate level of confidence:** If genetic testing not available for the patient, Affected sibling with BBS (with genetic testing +ve) + at least 2 primary criteria **High level of confidence:** **Child's genetic testing +ve** At least 1 primary criteria OR If genetic testing not available, 4 primary criteria/ (3 primary + 2 secondary)
From 16 years old	**Primary** • Polydactyly • Obesity • Retinal dystrophy • Kidney dysfunction/abnormalities **Secondary** • Hypogonadism • Micropenis • Neurodevelopmental disability • Anosmia/hyposmia	**Moderate level of confidence:** If genetic testing not available for the patient, Affected sibling with BBS (with genetic testing +ve) + at least 2 primary criteria **High level of confidence:** **BBS gene testing positive** Retinal dystrophy + 1 other primary criteria OR If genetic testing not available: Retinal dystrophy + 3 primary criteria /(2 primary criteria+2 secondary criteria)

Abbreviations

BBS Bardet Biedle syndrome
DNA Deoxyribonucleic acid

Declarations

Conflict of interests

The authors declare no conflict of interests.

Patient Consent

Patient consent has been obtained.

Acknowledgement

None

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