

Bardet–Biedl Syndrome with Café-au-Lait Macule: Association or Coincidence?

Sir,

Bardet–Biedl syndrome (BBS) is a rare autosomal recessive ciliopathy characterized by retinal dystrophy, truncal obesity, postaxial polydactyly, renal dysfunction, learning difficulties, and hypogonadism.^[1]

An 8-year-old male child, born out of nonconsanguineous marriage, presented with dark-colored skin lesion over the neck and abdomen. The parents of the child gave history of diminished vision and difficulty in speech and learning. The child was admitted at the age of 7 days for polycystic kidney disease diagnosed by ultrasonographic findings. There was no history of skeletal deformity, neurological defects, or hearing impairment. There was no history of a similar dark-colored lesion in the family.

According to WHO growth chart, height was <2SD, weight was >1SD and resultant BMI was >3SD. On general examination, the height and weight of the patient were 114 cm (<3 standard deviation) and 30.2 kg (<2 standard deviation), respectively, with resultant body mass index of 23.2 (>2 standard deviation) [Figure 1]. Blood pressure was 110/70 mmHg and pulse rate was 78/min. Rest of the general and systemic examination was unremarkable.

On cutaneous examination, there were four well-defined, coffee-brown colored patches with regular borders. Among which, the largest patch was 3.5 × 4 cm in size over the abdomen, and there were other small patches over the neck and the trunk [Figure 2a and b]. There was postaxial polydactyly of the bilateral lower limb along with features of hypogonadism and micropenis [Figure 3a and b]. On ophthalmological examination, visual acuity of both the eyes was finger counting at half



Figure 1: An 8-year-old male obese child with a body mass index of 23.2 (>2 standard deviation)

a meter and was diagnosed as myopia. Color vision examination done by Ishihara chart after correction of refractive error revealed deuteranomaly. Fundus examination showed hyperpigmentation of macular dystrophy with foveal thinning and was suggestive of early changes of retinitis pigmentosa with macular cone-rod dystrophy [Figure 4].

A detailed psychiatric evaluation was suggestive of delay in linguistic, social, and

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intellectual milestones (IQ: 70), which was evident as difficulty in reading, writing, calculation, and poor conversation skills.

Routine investigations including blood sugar and lipid profile were within normal limits. Ultrasound of the abdomen revealed hyperechoic medulla of bilateral kidneys which was suggestive of healed polycystic kidney disease [Figure 5], and bilateral inguinal testis which was suggestive of undescended testis [Figure 6a and b]. Pure tone audiometry, chest radiograph, electrocardiograph,

and two-dimensional echocardiogram did not reveal any abnormalities. Histopathological examination of the large patch over lower abdomen revealed basal hyperpigmentation with increased focal basal melanocytes. On Masson Fontana stain, melanin content was increased in basal cell layer although pigment granules were normal in size. These findings were suggestive of café-au-lait macule (CALM) [Figure 7]. On the basis of history, clinical features, and investigations, a diagnosis of BBS with CALM was made. The patient was referred to a psychiatrist, pediatric surgeon, and dietician for further management. Ophthalmologist advised glasses for the refractive error.



Figure 2: (a and b) Well-defined, coffee-brown colored patches with regular borders, with the largest patch (3 × 54 cm in size) seen over the abdomen and other small patches seen over the neck and trunk



Figure 3: (a and b) Postaxial polydactyly of the bilateral lower limb along with features of hypogonadism and micropenis



Figure 4: Fundus examination showed hyperpigmentation of macular dystrophy with foveal thinning, suggestive of early changes of retinitis pigmentosa with macular cone-rod dystrophy

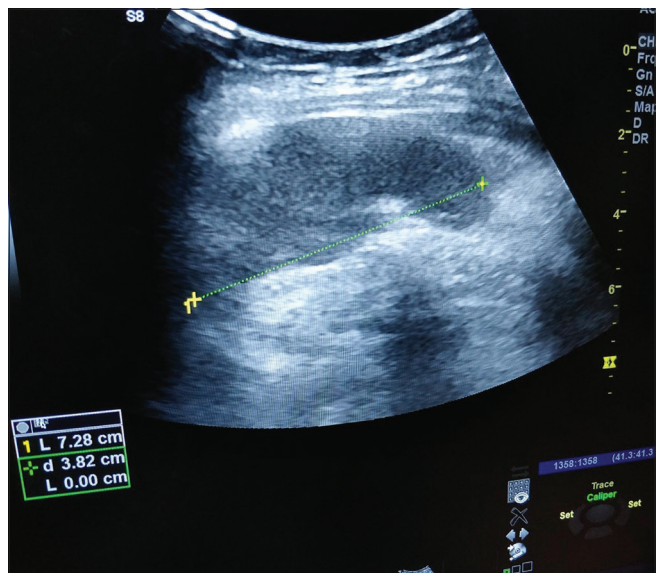


Figure 5: Ultrasound of the abdomen revealed hyperechoic medulla of bilateral kidneys which was suggestive of healed polycystic kidney disease

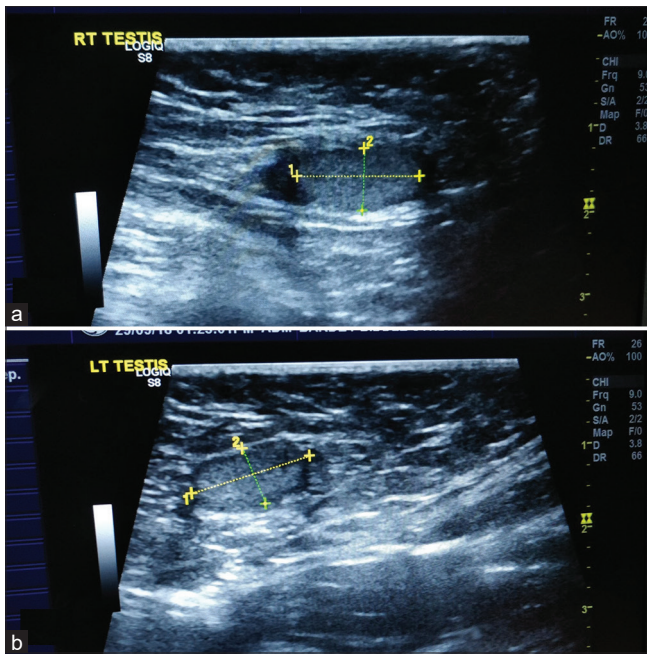


Figure 6: (a and b) Ultrasound of the abdomen revealed bilateral inguinal testis suggestive of undescended testis

BBS is named after Georges Bardet and Arthur Biedl. The first known case was reported by Laurence and Moon in 1866. BBS is a genetically heterogeneous disorder, with at least 20 disease loci identified from BBS1 to BBS20.^[2] Beales *et al.*, in the year 1999, modified the diagnostic criteria for BBS [Table 1].^[3] Presence of four primary features or a combination of three primary features plus two secondary features is diagnostic of BBS.^[3] Our patient had all of the six primary features and two secondary features, i.e., speech delay and developmental delay, thus supporting the diagnosis of BBS. Dental anomalies, anosmia, hepatic, and cardiac abnormalities were absent in our case.

Although BBS affects many tissues and organs, skin and its adnexa seem seldom to be involved. Mucocutaneous manifestations, sporadically described in association with BBS, are purpura, anocutaneous fistula, multiple melanocytic nevi (in up to 20% of patients),^[4] lymphangioma, and gingival hyperplasia.^[5]

Solitary CALMs are seen in 2.5% of normal neonates and up to 25% of preschool children, however, the presence of two or more CALMs is quite infrequent and usually associated with some syndrome complex.^[6] The molecular genetics of BBS involves activating mutations of the mTOR pathway through regulation of various genes.^[7] An activated mTOR signaling is also associated with decreased mitogen-activated protein kinase activity, which in turn is implicated in increased melanogenesis.^[8] Thus, the occurrence of CALMs in BBS can be explained on the basis of this hypothesis. However, this needs future molecular analysis for confirmation.

There is still no targeted treatment for BBS, a multidisciplinary approach is required to effectively

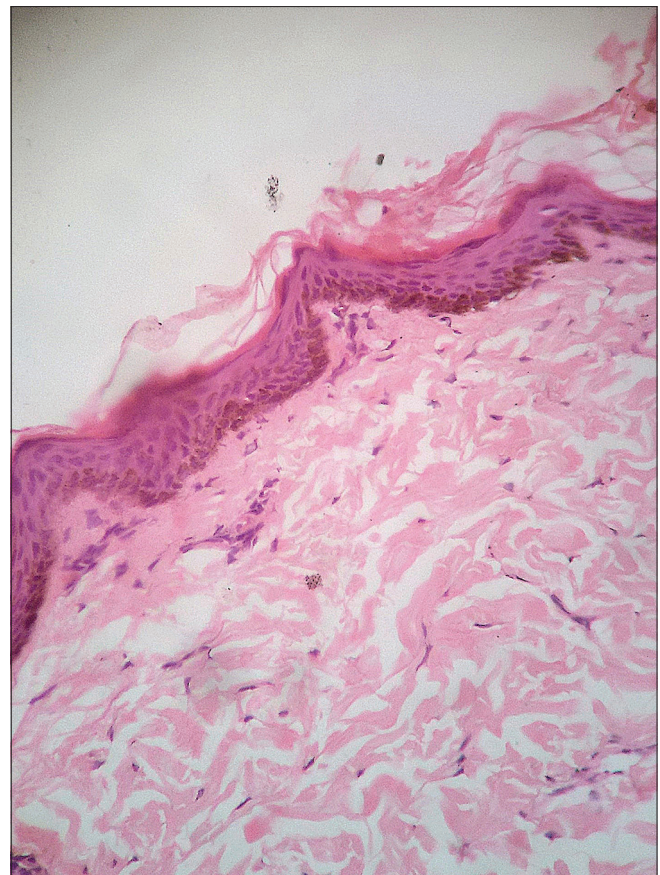


Figure 7: Histopathological examination of the large patch over lower abdomen revealed basal hyperpigmentation with increased focal basal melanocytes which were suggestive café-au-lait macule (H and E, 40x)

Table 1: Modified diagnostic criteria for BBS (Beales *et al.*)^[3]

Primary features	Secondary features
Rod-cone dystrophy	Speech delay/disorder
Polydactyly	Strabismus/cataract/astigmatism
Obesity	Brachydactyly/syndactyly
Learning disabilities	Developmental delay
Hypogonadism in males	Polyuria/polydipsia
Renal anomalies	Ataxia/ Poor co-ordination
	Mild spasticity
	Diabetes mellitus
	Dental crowding/hypodontia/high arched palate
	Hepatic fibrosis
	Left ventricular hypertrophy

manage this pleiotropic condition since birth. A long-term follow-up is needed in all cases to look for metabolic, ophthalmic, renal, and cardiac complications. We report a case of an 8-year-old male child with CALM in case of BBS. To our knowledge, such association has not been reported in the literature, which makes it ambiguous and intriguing. Electrophysiology or genetic testing for the diagnosis of retinal dystrophy was not done due to lack of resources, which is a limitation in our case.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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