An infant with polydactyly and renal anomalies: early diagnosis of a rare syndrome

Daniella Magen, Nathan Ish-Shalom, Abraham Lorber, Asaad Khoury and Israel Zelikovic

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Case

A 3-week-old male infant was referred for evaluation of multiple congenital anomalies and failure to thrive. He is the fourth offspring of first degree cousins of Arab–Muslim origin. Family history was notable for obesity, learning difficulties, reduced kidney function and visual impairment in a 10-year-old brother. The infant, weighing 3.3 kg, was born after an uneventful pregnancy at full term by spontaneous delivery. On admission he appeared malnourished and weighed 3.1 kg. No facial dysmorphism was present (Figure 1). There was postaxial polydactyly of all four limbs (Figures 2 and 3). Tachypnea and dyspnea were noted, and a grade 3/6 systolic heart murmur was heard over the entire precordium. Blood pressure was normal in all four extremities. Examination of the external genitalia revealed micropenis (Figure 4) and palpable testicles of normal size. Ophthalmologic evaluation including fundoscopy was unremarkable.

Serum blood urea nitrogen and creatinine levels were elevated (40 and 0.9 mg/dl, respectively). Other blood chemistries were unremarkable.

Chest X-ray showed cardiomegaly. Echocardiography revealed both atrial and ventricular septal defects, a hypoplastic aortic arch and a tubular aortic coarctation. Abdominal sonogram revealed left renal crossed ectopy (Figure 5). Both kidneys were small for age, hyperechogenic, and showed no cortico-medullary differentiation. Brain ultrasonography was unremarkable.

The combination of postaxial polydactyly and renal, cardiac and genital malformations in an offspring of consanguineous parents, in conjunction with a sibling suffering from obesity, renal failure, mental retardation and visual impairment, have led us to diagnose Bardet–Biedl syndrome (BBS) in this young infant.

Discussion

BBS is a rare autosomal recessive disorder, characterized by obesity, pigmentary retinopathy, mental retardation, hypogenitalism, postaxial polydactyly and renal malformations. Other common manifestations include cardiac malformations, hypertension and diabetes mellitus.

The syndrome was independently described by Bardet and Biedl in the 1920s [1,2]. It was later erroneously coupled with another disorder described by Laurence and Moon, and was consequently referred to as Laurence–Moon–Biedl syndrome. Based on differences in clinical characteristics, BBS and Laurence–Moon syndrome are now recognized as separate disorders [3].

The prevalence of BBS, generally considered a rare disorder, is 1 : 160,000 in Europe. However, its prevalence is markedly increased in highly consanguineous Arab-Bedouin communities in the Middle East (1 : 13,500), and in Newfoundland, Canada [4].

There is considerable heterogeneity and intrafamilial variation in the extent and severity of clinical manifestations of BBS. Obesity, mainly of the trunk and proximal limbs, is one of the most common features. It develops in early childhood and is aggravated with age. Ocular manifestations are also...
common and become apparent between the ages of 4 and 10 years. They include retinal dystrophic changes leading to abnormal electroretinogram, decreased night vision, reduced visual acuity and blindness at a young age. Mild to moderate mental retardation is an additional feature of the syndrome. The frequency of mental retardation and its severity vary between reports. Hypogonadism in affected males is common. Most affected men have small external genitalia with primary testicular failure. In females, however, hypogonadism is less frequent, and normal fertility has

Fig. 1. General appearance of the infant. Subcutaneous fat tissue is sparse. No facial dysmorphism is seen.

Fig. 2. Postaxial polydactyly of both hands.

Fig. 3. Postaxial polydactyly of both feet, with partial syndactyly of the second and third toes of the right foot.

Fig. 4. External genitalia with micropenis.
been reported. Dysmorphism of extremities, including postaxial polydactyly, syndactyly or brachydactyly, is one of the earliest and most common manifestations of BBS. Renal involvement is observed in most affected individuals. It consists of structural and functional abnormalities such as calyceal or pelvic dilatation, fetal lobulation, and focal and diffuse cortical loss, as well as tubular dysfunction, hypertension and progressive renal failure [5,6]. Cardiac anomalies in BBS include various valvular malformations, thickening or defects of the interventricular septum, and hypertrophic cardiomyopathy [7]. The prognosis of patients with BBS is generally poor. Their survival and quality of life depend on the severity of clinical features, as well as on the quality of the medical care they receive [8].

BBS is an autosomal recessive disorder characterized by non-allelic heterogeneity. Genetic analysis has mapped the disease to several independent loci, all of which produce similar phenotypes. Linkage analysis studies have so far identified six distinct loci responsible for the syndrome (BBS types 1 to 6, mapped to chromosomes 11q13, 16q21, 3p, 15q22.2-q23, 2q31 and 20p12, respectively) [4,9]. To date, only three of the six possible genes mutated in BBS have been identified, including: BBS2, which encodes a protein of unknown function; BBS4, which encodes a protein with homology to O-linked N-acetyl glucosamine transferase; and BBS6, which encodes a putative chaperone protein [10]. The remaining three BBS genes, as well as the biological functions of the BBS gene products responsible for the disorder, remain to be identified. It has been suggested that identification of the molecular and biochemical pathways involved in the pathogenesis of BBS may provide clues to the mechanisms underlying common disorders such as obesity, diabetes mellitus and mental retardation [10,11].

Most cases of BBS are diagnosed after the first decade of life [5]. Diagnosis in early infancy is very rare. Delay in diagnosis is probably related to the slow evolving nature of clinical features in this syndrome. In our case, the constellation of clinical findings in both infant and older sibling, combined with the family

Fig. 5. Renal sonogram showing left renal crossed ectopy, with both kidneys located in the right abdomen. The kidneys are small for age (length 4 cm) and hyperechogenic; mild pelvic dilatation is seen.
history of consanguinity has led to the diagnosis of BBS in the neonatal period. Early diagnosis of BBS may significantly improve the quality of medical care provided to patients with this syndrome and may increase their survival.

**Teaching points**

BBS is a rare genetic disorder, inherited as an autosomal recessive trait. Since in most cases the full-blown clinical picture does not evolve before the end of the first decade of life, diagnosis of the syndrome during early infancy is very rare. Nevertheless, this case illustrates that thorough clinical evaluation coupled with awareness of this rare syndrome can lead to the diagnosis of BBS in early life.

**References**