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Atrioventricular canal defect in Bardet-Biedl syndrome: Clinical evidence supporting the link between atrioventricular canal defect and polydactyly syndromes with ciliary dysfunction536

To the Editor:

Bardet-Biedl syndrome (BBS) is an autosomal recessive disorder characterized by obesity, retinitis pigmentosa, postaxial polydactyly, genito-urinary malformations, cognitive impairment, and congenital heart defect (CHD).[1] Molecular basis of BBS are complex. Genetic heterogeneity is demonstrated by the identification of nine different BBS genes (BBS1–BBS9) cloned in the genome.[2–12] Additionally, the genetic interaction between different loci was suspected to be involved, and triallelic inheritance has been demonstrated in several instances.[13,14]

The BBS phenotype overlaps with clinical manifestations of many syndromes. For example, a recessive mutation in a BBS gene has been recently identified in six fetuses clinically diagnosed as having Meckel or "Meckel-like" syndrome, demonstrating that the antenatal presentation of BBS may mimic Meckel syndrome.[15] Meckel syndrome is a fetal-lethal condition presenting with renal cysts, hepatic fibrosis, postaxial polydactyly, and occipital encephalocele.[16,17] The clinical diagnosis of BBS generally becomes clear during childhood, in concomitance with the development of obesity and retinal dystrophy as characteristic "markers" of the syndrome. The evolution of the phenotype with time makes the concept of clinical overlap of BBS with other condition not new. In fact, it has been previously shown that the BBS phenotype overlaps with clinical manifestations of McKusick-Kaufman syndrome,[3,18,19] an autosomal recessive condition characterized by hydrometrocolpos, postaxial polydactyly and CHD.[20,21] The phenotypic overlap between BBS and McKusick-Kaufman syndrome has been recognized, following the observation that infants initially diagnosed with McKusick-Kaufman syndrome, owing to the presence of polydactyly and vaginal abnormalities, develop later obesity and retinal dystrophy, resulting in the diagnosis of BBS.[18,19] As occurring for Meckel syndrome,[15] molecular studies demonstrated that mutations in McKusick-Kaufman syndrome gene cause a subset of BBS patients.[2,3]

CHD is occasionally found in patients with BBS,[1] although studies on CHDs in BBS are effectively rare and very old, mostly published before the cloning of several BBS genes.[1,22,23] The CHDs more frequently found in BBS were aortic valve anomalies, atrial septal defect, pulmonary stenosis, and dilated cardiomyopathy.[1,22,23] Hypertrophy of the left ventricle was often reported as acquired cardiac defect due to renal disease and systemic hypertension.[22] Nevertheless, accurate review of published reports of BBS and overlapping BBS-McKusick-Kaufman syndrome shows that atrioventricular canal defect (AVCD) is the prevalent CHD,[15,19,20,24,25] and dextrocardia without structural cardiac defects and abdominal situs inversus have also been described.[8,26,27] Additionally, polysplenia in the setting of heterotaxia has been reported in two sibs with BBS described by McLoughlin et al.,[28] although the diagnosis of BBS was questioned for these patients.[29] Moreover, dextrocardia in the setting of situs inversus has been described in Meckel syndrome,[30,31] and in "Meckel-like" syndrome.[32–34] Additionally, we observed a patient with BBS and AVCD, which was included in our personal series of 14 patients with AVCD and postaxial polydactyly.[24,35] Clinical features of this patient included macrocephaly, obesity, retinal dystrophy affecting periphery and the macular area, a post-minimus postaxial polydactyly of right hand and complete postaxial polydactyly of right foot with a well-formed toe, mild mental retardation, and CHD. Echocardiography showed viscero-atrial situs solitus with levocardia, concordant atrioventricular and ventriculo-arterial connections, and a partial form of AVCD with double mitral orifice.

Thereafter, AVCD and laterality defects seem to be an important clue for the diagnosis of BBS in some cases. Actually, a possible association of cardiac malformations with syndromes with postaxial polydactyly is well-known, and published reports demonstrated a specific link with AVCD and cardiac malformations usually occurring in heterotaxia.[35,36] The association between AVCD with or without common atrium is rare in the non-syndromic patients, while it is characteristic of heterotaxia syndrome with asplenia[37] or polysplenia.[38] CHDs in heterotaxia include AVCD, common atrium, anomalous systemic and pulmonary venous drainage, persistent left superior vena cava with unroofed coronary sinus, and conotruncal defects.[37,39] Among syndromes with postaxial polydactyly, the combination of AVCD and common atrium is particularly frequent in the oral-facial-digital syndromes, in short rib-polydactyly syndromes including Ellis-van Creveld syndrome, and in their related transitional phenotypes (Table 1).[35] On the other hand, the association of AVCD and anomalous pulmonary venous return is specifically associated with Smith-Lemli-Opitz syndrome (Table 1).[36,40]

Recent experimental evidences regarding BBS are intriguing in regard to CHD and situs abnormalities. In fact, a role for several BBS proteins in regulating ciliary function has been demonstrated.[10,11,41,42] It must be noticed that many clinical aspects of BBS can be explained by a ciliary defect. The finding of AVCD as partial manifestation of heterotaxia in some patients with BBS is in agreement with the involvement of BBS proteins in ciliary function, since dysfunction of the nodal cilium is known to cause left-right axis defects in vertebrates.[43,44]

Interestingly, it has recently been demonstrated that knockout male mouse embryos lacking the gene of oral-facial-digital syndrome type 1 (*Ofd1*) have failure of left-right axis specification with abnormal cardiac tube retaining a midline position or reversal of the heart loop.[45] Ultrastructural analysis showed a lack of cilia in the embryonic node, and a specific role for the Ofd1 protein in cilium assembly through basal body dysfunction has been demonstrated.[45] As an additional observation, the *MKS1* gene has recently found to be mutated in families with Meckel syndrome linked to 17q, and comparative genomic and protemics data implicate MKS1 in ciliary functions.[46]

Table 1
Syndromes associating atrioventricular canal defect (AVCD) and postaxial polydactyly

Syndrome	Type of AVCD	Extracardiac features	Gene
Bardet Biedl syndrome	Partial AVCD	Obesity	*BBS1-BBS9*
		Retinitis pigmentosa	
		Postaxial polydactyly	
		Genito-urinary malformations	
		Mental retardation	
Ellis-van Creveld syndrome	Partial AVCD with common atrium	Short-limb dwarfism	*EVC1-EVC2*
		Oral frenula	
		Oligodontia	
		Short ribs	
		Postaxial polydactyly	
		Small nails	
Meckel syndrome	Partial AVCD	Occipital encephalocele	*MKS1-MKS3*
		Cleft lip/palate	
		Polycystic kidneys	
		Hepatic fibrosis	
		Postaxial polydactyly	
		Mental retardation	
Oral-facial-digital syndromes	Partial AVCD with common atrium	Lobulated tongue	*Ofd 1*
		Oral frenula	Other unknown genes
		Cleft palate	
		Postaxial polydactyly	
Smith-Lemli-Opitz syndrome	Partial AVCD with abnormal pulmonary venous return	Facial anomalies	*DHCR7*
		Microcephaly	
		Cleft palate	
		Hypospadia	
		Toe syndactyly	
		Mental retardation	

In conclusion, AVCD and laterality defects seem to be an important feature for early diagnosis of BBS. Ciliary dysfunction may have a fundamental role in determining specific cardiac phenotypes in several syndromes with postaxial polydactyly and CHD. Mutations in proteins necessary for cilium formation and functionality must be considered when investigating syndromes with postaxial polydactyly and cardiac laterality defects.

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