CLINICAL QUIZ (p153) ANSWER

What is the diagnosis?

Retinal cone-rod dystrophy, central obesity, postaxial polydactyly and cognitive impairment are some of the cardinal features of Bardet-biedl syndrome (BBS) (MIM #209900). With the diagnosis in mind, targeted genetic testing was arranged and revealed compound heterozygous pathogenic variants in *BBS2* {NM_031885.3} c.534+1G>T (p.?); c.1237C>T (p.Arg413*). The molecular diagnosis of BBS is therefore substantiated.

What are the clinical features?

BBS is an autosomal recessive non-motile ciliopathy with multisystem involvement and variable expressivity. Commonly reported clinical features include retinal cone-rod dystrophy, obesity, postaxial polydactyly, developmental delay, endocrine and genitourinary anomalies. Early diagnosis is challenging as genitourinary malformations and polydactyly may be the only presenting features in infants with BBS.

Retinal cone-rod dystrophy is the most penetrant feature in BBS and is reported in 94% of patients.[1] Other ophthalmologic presentations, including cataracts, astigmatism and strabismus, have also been described. BBS patients often present with night blindness followed by progressive peripheral visual impairment and overall loss of visual acuity due to retinal dystrophy in their first decade of life.[2] By the second or third decade of life, affected individuals are often legally blind.

The majority of BBS affected individuals have a normal birth weight. However, postnatal central obesity is common in the first year of life, which is frequently complicated with obesity related metabolic complications, including hypertension and type 2 diabetes mellitus. Hypogonadism presented with delay in puberty and infertility is common, although some of the affected individuals are reported to have biological children. 59% of BBS patients are reported to have hypogonadism and variable genitourinary abnormalities. Micropenis, small testis and cryptorchidism are frequently reported in affected males, while genitourinary malformations such as hypoplastic fallopian tubes or ovaries, hypoplastic or duplex uterus, absent vaginal and / or urethral orifice, partial or complete vaginal atresia etc. have also been reported in female individuals with BBS.

Affected individuals may have variable renal involvement with progressive renal parenchymal disease or structural anomalies such as duplex kidney, horseshoe kidney and dysplastic cystic disease etc. Chronic kidney disease is a major cause of morbidity and mortality, with up to 6-8% of affected individuals develop end-stage renal disease requiring dialysis or transplantation.[3]

Developmental delay and cognitive impairment are reported in up to 66% of individuals.[1] However, this figure may be overestimated as the mild developmental delay in some individuals may be attributed to the underlying visual impairment. Attention problem and autistic spectrum disorder related features are reported in up to 69% and 77% of individuals with BBS respectively, while ataxia, poor coordination and epilepsy have also been described.[4]

Olfactory dysfunction is postulated to be related to underlying olfactory cilia defects and is been reported in 47-100% of BBS patients.[5,6] Digit anomalies including postaxial brachydactyly and syndactyly are detected in 79% of affected BBS patients.[1] Various dysmorphic features including macrocephaly, brachycephaly, short and downslanting palpebral fissures, malar hypoplasia etc. have been reported in various affected individuals but may be subtle and inconsistent.

What is the genetic basis of BBS?

BBS is an autosomal recessive disorder belonging to a large group of ciliopathic diseases. It can be caused by loss-of-function mutations in at least 26 different genes.[1] A precise molecular diagnosis often requires a multigene panel as there is significant overlap in clinical and molecular findings between BBS and other ciliopathies. Some genotype-phenotype correlations exist but they are not absolute. Variants in one of the eight genes encoding different subunits of the octameric protein complex (BBS1/2/4/5/7/8/9/18), collectively known as BBSome, accounted for more than 50% of molecularly substantiated BBS.[7]

What are the management issues for BBS?

A multi-disciplinary approach is required for the management and follow-up of BBS patients. Regular evaluation by an ophthalmologist for potential visual impairment and strabismus is recommended. Interval neurocognitive assessment for developmental delay is required. Periodic monitoring of liver, renal functions and abdominal ultrasound imaging is necessary because of an increased risk of developing liver fibrosis, steatosis and renal parenchymal diseases in affected individuals. Regular surveillance of growth parameters, including head and waist circumference, height and weight etc. are recommended. Lipid profile, fasting glucose and HbA1c should be checked regularly from the age of 4 years old for potential metabolic syndrome association. Dietary modifications for obese individuals and regular exercising are recommended. Regular evaluation for signs and symptoms of obstructive sleep apnea is necessary, especially in obese individuals. Interval endocrine assessment is also recommended due to an increased risk of hypogonadism and hypothyroidism. Surgical correction may be required for structural anomalies such as congenital heart disease, polydactyly, genitourinary malformations etc.

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