Bardet-Biedl Syndrome

Bardet-Biedl syndrome (BBS) is an autosomal recessive multisystemic genetic disorder characterised by six major defects including obesity, learning disability, renal anomalies, polydactyly, retinal degeneration and hypogenitalism.\(^1\)

19 BBS genes have been identified to date. The underlying pathophysiology involves a complex interaction between genetic factors and ciliary dysfunction. When major dysfunction of the renal tubule cilia is involved, renal failure is a predominant feature and a leading cause of BBS mortality.\(^2\)

Epidemiology\(^{3, 4}\)

BBS is a familial condition.

- The prevalence in most of North America and Europe is 1 in 140,000 to 1 in 160,000 newborns.\(^5\)
- Bedouins and the Arab population of Kuwait have an incidence of 1:13,500.
- A high incidence (1:17,500) is also found in Newfoundland.
- Ratio of male:female is approximately 1.3:1.

Genetics

BBS is a genetically heterozygous disorder with 19 genes described so far (BBS1 to 19). All BBS genes are related to cillum biogenesis and/or function.\(^6\)

Inheritance is autosomal recessive but unaffected siblings carrying two mutations have been reported in BBS families. The affected child in such families was found to have a third mutation. Other studies have reported a more severe phenotype in those carrying the third mutation suggesting the possible effect of modifier allele. This has been called 'tri-allelic inheritance', or 'recessive inheritance with a modifier of penetrance'.\(^3\)

Nineteen forms have been identified with differing phenotypes.\(^7\) The mutation spectrum varies between different populations. In the European and Caucasian population the most commonly involved BBS genes are BBS1 and BBS10, while in the Saudi population they are BBS1, BBS3 and BBS4.

There is no clear correlation between the genotype and clinical expression of BBS. Some BBS gene mutations (eg, BBS1) have been found to be associated with a milder phenotype.\(^8\)

NB: Laurence-Moon-Biedl syndrome and Laurence-Moon-Biedl-Bardet syndrome are no longer considered valid terms because the patients of Laurence and Moon had paraplegia but no polydactyly and obesity, which are the main characteristics of BBS.\(^9\)

Clinical features\(^{10}\)

BBS is diagnosed if at least four of the main manifestations are present. Alternatively, presence of three major and two minor or secondary criteria, as described by Beales et al, can be used to make the diagnosis.\(^9\)

Diagnosis during infancy can be difficult as not all the features are present and some develop during late childhood.
The major clinical features are:

- **Retinal degeneration** - rod-cone dystrophy occurs in 90-100% of cases and leads to severe visual handicap with total blindness occurring before the second decade of life. Visual acuity is decreased to begin with along with impaired colour vision and decreases progressively.
- **Obesity** - with an estimated incidence of 72-92%, obesity begins early in childhood and becomes severe with age. It is widespread and diffuse and some patients develop type 2 diabetes.
- **Polydactyly-type limb anomalies** - these may be the only feature present at birth and are reported in 63-81% of patients. It is usually post-axial and may be associated with other limb defects, including brachydactyly and syndactyly for both hands and feet.
- **Hypogonadism and genital anomalies** - these are reported in 59-98% of patients and may manifest as delayed puberty or hypogenitalism in males and genital abnormalities in females (eg, hypoplastic Fallopian tubes and uterus or vaginal atresia).
- **Cognitive impairment** (50-61%) - learning difficulties, speech deficits and behavioural problems, including autistic traits and psychosis, have all been described.
- **Renal abnormalities** (20-53%) - these include cystic tubular disease and anatomical malformations. Chronic kidney disease is one of the major causes of mortality and morbidity in BBS.

Minor (secondary) clinical features include speech delay, developmental delay, diabetes mellitus, dental anomalies, congenital heart disease, brachydactyly/syndactyly, ataxia/poor co-ordination, deafness and anosmia/hyposmia.

**Differential diagnosis**

- **Laurence-Moon syndrome** (in which affected individuals have a spastic paraparesis but no polydactyly).
- **Cohen's syndrome** (a genetic disorder involving developmental delay, intellectual disability, microcephaly, progressive myopia and retinal dystrophy).
- **Alström’s syndrome** (a genetic condition featuring paediatric cone-rod dystrophy, obesity and deafness).
- **McKusick-Kaufman syndrome** (a genetic disorder involving polydactyly, congenital heart disease and fluid in the pelvis).

**Investigations**

- Diagnosis is usually made on the basis of the clinical features but should be confirmed by molecular genetic testing whenever possible.
- Genotyping may be required to differentiate BBS from other rare genetic disorders.
- Molecular analysis can be challenging because of clinical and genetic heterogeneity. Recently the implementation of next-generation sequencing has accelerated the molecular analysis of BBS patients.

**Management**

A thorough initial evaluation to determine the extent of disease and the individual’s needs should be done once the diagnosis is made. This includes:

- Ophthalmological evaluation including visual acuity, visual fields and fundoscopy.
- Examination of genitalia and pelvic ultrasound to assess internal organs.
- BMI calculation and dietary assessment.
- Renal function studies and renal ultrasound.
- BP measurement and cardiac evaluation including ECG and echocardiogram.
- Developmental evaluation.

There are no specific treatments for the characteristics associated with BBS.

- As vision worsens, individuals will benefit from the use of low-vision aids and orientation as well as from mobility training.
- To manage the complications of renal disease, every individual with the disorder should be evaluated and managed by a nephrologist.
Complications of obesity (e.g., diabetes and hyperlipidaemia) may need to be addressed. Diet, exercise and behavioural therapies may be needed to manage obesity. Excision of accessory digits may be necessary to improve function and facilitate the fitting of footwear.

**Prognosis**[2]

Prognosis is very poor where renal failure occurs.

**Prevention**[4]

- Genetic counselling and pre-conception genotyping of family members may be worthwhile if the genetic mutation has been identified in a family member.
- Prenatal second-trimester ultrasound scanning in pregnancies with increased risk looking for polydactyly and renal anomalies (enlarged hyperechoic kidneys) can help in diagnosing BBS antenatally.

**Further reading & references**

- RP Fighting Blindness
- Bardet-Biedl Syndrome 1, BBS1; Online Mendelian Inheritance in Man (OMIM)
- Waters A et al; Bardet-Biedl Syndrome, Gene Reviews, 2011.
- Phenotype entries for Bardet-Biedl syndrome; Online Mendelian Inheritance in Man (OMIM)

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