Management of Bardet-Biedl Syndrome

A Clinical Guideline

Bardet-Biedl Syndrome Guideline Development Group

www.euro-wabb.org

European Commission

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Introduction...

… to Bardet-Biedl Syndrome

Bardet-Biedl syndrome (BBS) is a rare disease with prevalence of about 1:100,000 (North America). BBS is characterized by rod-cone dystrophy (>90%), truncal obesity (72%), postaxial polydactyly, cognitive impairment, male hypogonadotrophic hypogonadism, renal abnormalities, and variable complex female genitourinary malformations. The visual prognosis for children with BBS is poor with mean age of legal blindness of 15 years. Significant weight gain begins within the first year and becomes a lifelong issue for most individuals. A majority of individuals have significant learning difficulties, but only a minority have severe impairment on IQ testing. Renal disease is a major cause of morbidity and mortality. The diagnosis of BBS is established by clinical findings. Multiple genes are known to be associated with BBS: BBS1, BBS2, ARL6 (BBS3), BBS4, BBS5, MKKS (BBS6), BBS7, TTC8 (BBS8), BBS9, BBS10, TRIM32 (BBS11), BBS12, MKS1 (BBS13), CEP290 (BBS14), WDPCP (BBS15) SDCCAG8 (BBS16) and LZTFL1 (BBS17). BBS is typically inherited in an autosomal recessive manner, but up to 30% of patients do not have identifiable mutations in known genes. Both interfamilial and intrafamilial phenotypic variability exists. Carrier testing and prenatal testing are possible if the disease-causing mutations in a family are known.

… to the Bardet-Biedl syndrome guideline project

The guidelines have been developed by referring physicians and geneticists involved in the EURO-WABB project, according to the DYSCERNE guideline development process (www.dyscerne.org.dysc.home/. The experts who participated to the guideline development are listed on page 20.

… to the Bardet-Biedl syndrome clinical management guidelines

What are the aims of the guidelines ?

The guidelines aim to provide recommendations for the diagnosis, the management and the follow-up of patients with BBS. As it is a multisystemic disorder, BBS patients may require various tests, screening and multidisciplinary interventions at different stages of their lives. These recommendations aim to support high quality care for people with BBS in a format that is accessible to anybody who is involved in the care of these patients. Note that transition is a process which includes the event of transfer from childrens' to adult services and needs to attend to the medical, psychosocial, and educational/vocational needs of the young person and his/her parents/carers. Care needs to be provided that includes attention to transition needs.

How they are organised ?

The guidelines are divided into

- clinical features and diagnostic criteria
- baseline investigations
- any recommended tests, that are listed and organised into specific groups corresponding to the different symptoms and affected organs. Any recommendations that are specifically addressed either to children or to adult patients are specified.

A list of references starts on page 16, organised according to the different sections of the guidelines.

Additionally, there is a list of useful contacts for patients and families affected by BBS, on page 21.

Note: N=normal; ABNL= abnormal

Diagnosis and clinical features of Bardet-Biedl Syndrome

Diagnostic criteria of BBS

Beales et al [1999 and 2001] have suggested that the presence of four primary features or three primary features plus two secondary features is necessary for diagnosis:

Primary Features	Secondary Features
Rod-cone dystrophy	**Speech delay/disorder**
Postaxial polydactyly	**Developmental delay**
Truncal obesity	**Behavioral abnormalities**
Learning disabilities	**Eye abnormalities** include strabismus, cataracts, and astigmatism
Hypogonadism in males	**Brachydactyly/syndactyly**
or **genital abnormalities** in females	**Ataxia/poor coordination/imbalance**
Renal disease	**Mild hypertonia** (especially lower limbs)
	Diabetes mellitus
	Orodental abnormalities
	Cardiovascular anomalies
	Hepatic involvement
	Craniofacial dysmorphism
	Hirschsprung disease
	Anosmia

Note: The diagnosis is established in individuals of all ages in whom two pathological mutations in the same BBS gene are identified. Cases have been reported of tri-allelic inheritance.

Recommended baseline investigations in Bardet-Biedl Syndrome

Clinical Features of BBS	Baseline investigations
Rod-cone dystrophy	Ophthalmologic evaluation, electroretinogram, visual field testing, fundus examination, ERG, OCT.
Orthopedic abnormalities	Note postaxial polydactyly, facial dysmorphism, dental abnormalities and pes planus with varus deformity and frequent genu valgum on physical examination
Obesity	Measurement of weight and height; calculation of body mass index (BMI)
Hypogonadism or **genital abnormalities**	Examination of the external genitalia in both sexes.
Insulin resistance/ diabetes mellitus	Fasting plasma glucose, even in infancy; glucose tolerance test (GTT) > age 6years Fasting plasma insulin concentration, as hyperinsulinemia may be present from infancy
Hyperlipidemia	A fasting lipid profile, including triglycerides
Renal and Urologic disease	Ask about urinary symptoms. Baseline blood pressure; 24-hour blood pressure monitoring Measurement of plasma urea and electrolytes, GFR. Renal ultrasound
Neurologic manifestations **Anosmia**	Neurologic examination. Consider smell identification test
Bilateral sensorineural hearing loss	Audiometry with auditory brain stem response (ABR) and otoacoustic emissions (OAE); assessment for otitis media and conductive hearing loss
Cardiovascular anomalies	Auscultation, ECG, Echocardiography
Hepatic disease	Measurement of plasma ALT, AST, and GGT concentration ; Liver ultrasonography
Confirmation of BBS diagnosis	
Molecular Analysis	Testing of genes known associated with BBS: BBS1, BBS2, ARL6 (BBS3), BBS4, BBS5, MKKS (BBS6), BBS7, TTC8 (BBS8), BBS9, BBS10, TRIM32 (BBS11), BBS12, MKS1 (BBS13), and CEP290 (BBS14) +/- Mutations in WDPCP (BBS15)

Recommendations for the management of Bardet-Biedl Syndrome
Sensory involvement

Visual assessment : **Cone-rod dystrophy**

At diagnosis in childhood

- Ophthalmologic assessment with visual acuity (nystagmus, strabismus, dark adaptation, refraction : astigmatism/high myopia)
- Visual field testing (peripheral loss initially)
- Fundus examination (Atypical pigmentary retinal dystrophy with early macular involvement)
- Electroretinography (ERG) testing indicated from 4 years of age
- OCT scan if suspected macular edema, VEP for differential diagnosis

ABNL

Follow up

Yearly eye examination:
- Visual acuity (loss of 3 degrees per year during adolescence, <20/200 by the 2nd to 3rd decade)
- Visual field testing (typically abnormal by10y)
- Fundus examination (Retinal photography for later comparison)
- ERG
- Screen for cataract and glaucoma

ABNL

Correction of refractive error (myopia, astigmatism), tinted glasses (if photophobia)
Use of low vision aids and mobility training (magnifying glasses, digital systems, voice systems).
Educational planning.
Cataract surgery if needed.

Hearing assessment: **Progressive bilateral sensorineural hearing loss**

At diagnosis

Audiogram / audiometry, tympanogram

ABNL

Auditory evoked potentials

Follow up

Yearly examination : audiometry
Detect glue ear (acute and chronic otitis media): can lead to an additional conductive hearing loss

ABNL

Prompt treatment for acute and chronic otitis media
Management in standard way by a specialist (myringotomy tubes and/or hearing aids)

Recommendations for the management of Bardet-Biedl Syndrome
Renal involvement

Renal malformations and abnormal renal function leading to end stage renal disease (ESRD)

Structural renal abnormalities and Functional renal disease

At diagnosis

- Ask about symptoms of anemia, polyuria, and polydipsia
- Baseline blood pressure assessment; 24-hour blood pressure monitoring
- Measurement of plasma creatinine, urea, electrolytes, GFR.
- Bladder and renal ultrasound examination (calyceal or parenchymal cysts, fetal lobulation and diffuse cortical scarring, unilateral agenesis, renal dysplasia, cystic tubular disease, upper tract malformations > glomerular disease, lower urinary tract malformations, detrusor instability).

Follow up

- Yearly for symptoms, baseline blood pressure +/-24h blood pressure monitoring
-Yearly early morning urine analysis for albumin creatinine ratio and dipstick testing for microscopic haematuria
- Yearly monitoring of plasma creatinine, urea and electrolytes, GFR

ABNL

Referral to a nephrologist
- Follow-up renal ultrasonography if structural renal malformation
- Regular monitoring of plasma creatinine, urea, electrolytes and GFR
-Progressive renal impairment can lead to end-stage renal disease (ESRD) necessitating renal transplantation

Complications

- Decreased urine-concentrating capacity
- Renal tubular acidosis,
- Hypertension
- Renal calculi
- Vesico-ureteric reflux
- Recurrent renal colic and urinary tract infection
- Nephrogenic diabetes insipidus

Recommendations for the management of Bardet-Biedl Syndrome

Metabolism and Endocrine System

Truncal obesity	From the first year of life (usually normal birth weight) : - Clinical examination (Note relative hyperphagia, excessive weight gain, levels of physical activity) - Calculation of body mass index (BMI) : Obesity if > 95thcentile for age and sex (BMI>30 in adults)
Follow up	- Annually measurement of weight and height; calculation of BMI (plot on growth charts). - Dietary evaluation especially if obesity is present -Education and dietary measures (healthy, reduced calorie diet), regular exercise (allowing for visual impairment) and lifestyle measures from an early age.
Obstructive sleep apnoea	-Annual screening for sleep apnoea using a questionnaire; overnight oximetry if abnormal
Hypogonadotropic hypogonadism	- Examination of the genitalia in both sexes (hypogonadism common in males) - Hormone levels : testosterone (or oestradiol+prolactin), gonadotropins FSH and LH, inhibin B -Pelvic ultrasound examination (females). Complex genitourinary malformations can occur
ABNL	-Surgical correction
Hypercholesterolemia	- Yearly fasting lipid profile, including triglycerides -Annual liver function tests
Hypothyroidism	- Thyroid function testing: at diagnosis, then annually

Recommendations for the management of Bardet-Biedl Syndrome

Endocrine System

Insulin resistance / Type 2 Diabetes Mellitus

At diagnosis

- Fasting plasma glucose (FPG)
- Oral glucose tolerance test (OGTT) after age 12 years
- Fasting plasma insulin concentration, as hyperinsulinemia may be present from childhood

Follow up
in adolescence

- Promotion of healthy eating, physical activity and lifestyle within limits of visual impairment
- Annual fasting plasma glucose
- Note acanthosis nigricans (indication of insulin resistance/diabetes mellitus)

ABNL

Diagnostic criteria of diabetes

Fasting (at least 8 hours) Plasma Glucose (FPG) ≥ 7.0 mmol/L

Or

Casual postprandial blood glucose ≥ 11.1 mmol/L + symptoms of diabetes (polyuria, polydipsia and unexplained weight loss)

Or

2 hour PG ≥ 11.1 mmol/L in a 75-g oral glucose tolerance test

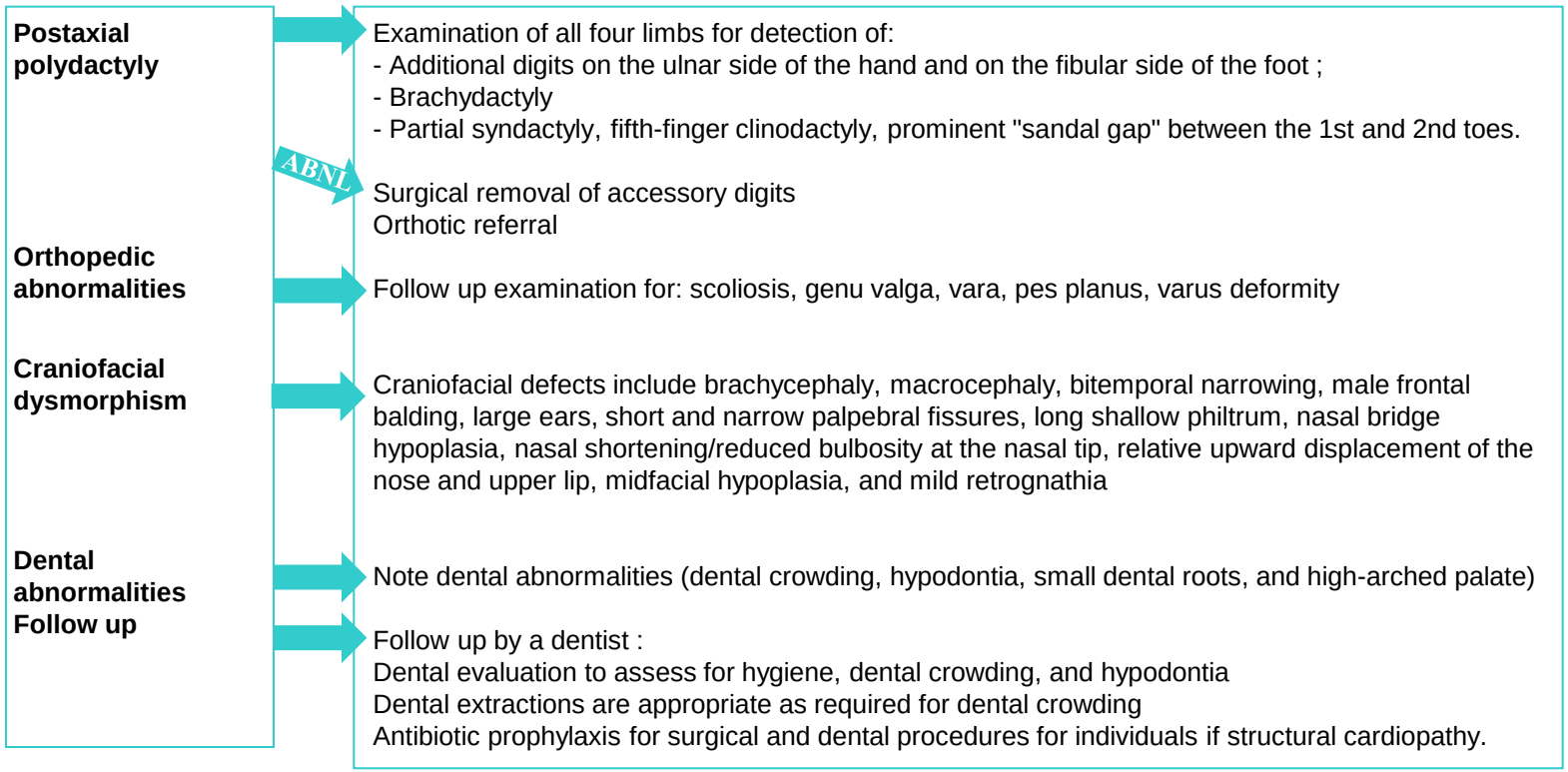
Recommendations for the management of Bardet-Biedl Syndrome
Neuro-cognitive involvement

Management by neurolodevelopmental paediatricians or clinical psychologists

Annual assessments for children

Developmental delay ++ Speech impairment		- Assessment of skills: language (intelligible speech and sentence formation may be delayed until age four years), motor skills (gross and fine) and psychosocial skills (interactive play/ability to recognize social cues).
	ABNL	- Speech therapy assessment - Consider videofluoroscopy and palatal articulation studies (pharyngeal and/or laryngeal muscles incoordination) -Early speech therapy should be offered at the first signs of speech delay and/or impairment.
Cognitive impairment		-Neuropsychological testing adapted to age and low vision and/or educational evaluation -
	ABNL	- Early clinical psychology intervention, assessment of special educational needs -
Mental health assessment		- Ask about anxiety, emotional immaturity, anger outbursts, disinhibition, depression, obsessive compulsive behavior, autistic spectrum disorder)
	ABNL	- Consider referral to psychiatric health services

Recommendations for the management of Bardet-Biedl Syndrome
Orthopedic and Dysmorphic features



Recommendations for the management of Bardet-Biedl Syndrome
Genetics

Locus heterogeneity with 17 genes known to be responsible for BBS: *BBS1, BBS2, ARL6 (BBS3), BBS4, BBS5, MKKS (BBS6), BBS7, TTC8 (BBS8), BBS9, BBS10, TRIM32 (BBS11), BBS12, MKS1 (BBS13), CEP290 (BBS14),SDCCAG8 (BBS16) and LZTFL1 (BBS17)* +/- Mutations in *WDPCP (BBS15)* (no evidence of pathogenicity)

Molecular Genetic testing

To confirm the diagnosis in a proband : diagnosis of BBS relies on clinical findings and family history
Molecular analysis:
- Screening for the M390R mutation in BBS1 (10-33% cases)
- Sequence analysis for genes BBS1, BBS2, BBS 6, BBS10 and BBS12 (responsible for 84% of published alleles)
- Sequence analysis of the rest of known BBS-related genes and for WDPCP.
- **Deletion/duplication analysis** for *BBS4, BBS5, BBS7*, and BBS9, and also for genes in which no deletions or duplications have been reported (*TRIM32, BBS1, BBS2, ARL6, MKKS, TTC8, BBS10, BBS12,* and *MKS1*).

Genetic counselling

1 or 2 mutated alleles : perform mutation screening in parents of index case and in affected relatives
Approximately 30% of persons with BBS do not have identified mutations
- Information about recurrence risk to parents (25%), to young adult patients who are affected, are carriers, or are at risk of being carriers and extended family members (++ before pregnancy). BBS is usually inherited in an autosomal recessive manner (multiallelic inheritance: fewer than 10%)
- Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family. Note: Carriers (heterozygotes) are asymptomatic (autosomal recessive disorder).

Prenatal Diagnosis

- Available only for families in which the disease-causing mutation has been identified
For pregnancies at increased risk for BBS (example : 25% recurrence risk for parents)
By analysis of DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling.
- Ultrasound examination in pregnancies at increased risk : to detect anomalies such as postaxial polydactyly and renal cysts (enlarged hyperechoic kidneys without corticomedullary differentiation should be considered recurrence of BBS).
- Ultrasound examination in pregnancies not known to be at increased risk. When antenatal ultrasonography reveals large hyperechoic kidneys with loss of corticomedullary differentiation in the presence of polydactyly a diagnosis of BBS or Meckel syndrome should be considered

Preimplantation Genetic Diagnosis

To discuss with referral centres (may be available for families in which the disease-causing mutation has been identified).

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Information for patients

Sources of information and support

The groups listed below are useful sources of support and information

•**Association BBS – Association Bardet Biedl**
Contact : M. Bertrand LASBLEIS - Tél. 33 (0)2 43 23 56 67 - Email. bertrand.lasbleis@wanadoo.fr

•**Lawrence-Moon-Bardet-Biedl society: www.lmbbs.org.uk**
The Society supports over 400 families and communicates with over 150 health professionals involved in their care.

•**Orphanet (www.orpha.net)**
Orphanet is an online database of rare diseases and related services provided through Europe. It contains information on over 5 000 conditions and lists specialised clinics, diagnostic tests, patient and organizations, research projects and clinical trials

•**OMIM (http://www.omim.org/)**
OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 12,000 genes. OMIM focuses on the relationship between phenotype and the entries contain copious links to other genetics resources.

• **RareConnect** (https://www.rareconnect.org/en)
RareConnect was created by EURORDIS (European Rare Disease Organisation) and NORD (National Organization for Rare Disorders) to provide a safe space where individuals and families affected by rare diseases can connect with each other, share vital experiences, and find helpful information and resources