Monitoring and follow up of Bardet-Biedl Syndrome

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The clinical diagnosis of Bardet-Biedl syndrome is made by the presence of 4 major features or 3 major and 2 minor features.

Table 1 Criteria for Diagnosis of Bardet-Biedl Syndrome

Major Features	Minor Features	Criteria for Diagnosis
Rod-cone dystrophy Polydactyly Central obesity Hypogonadotropic hypogonadism and/or genitourinary anomalies Renal anomalies Cognitive impairment	Speech delay Developmental delay Diabetes mellitus Dental anomalies Congenital heart disease Brachydactyly/syndactyly Ataxia/poor coordination Anosmia/hyposmia	• Four major features • Three major features and two minor features

Definite diagnosis is made by genetic tests.

Recommended investigations; baseline and follow up:

1-Ophthalmologic evaluation: electroretinogram, visual field testing, fundus examination then yearly consult

2-Orthopedic abnormalities: Note postaxial polydactyly, facial dysmorphism, dental abnormalities and pes planus with varus deformity and frequent genu valgum on physical examination

3-Obesity: Measurement of weight and height; calculation of body mass index (BMI) and waist-hip ratio and then annually evaluation

4-Hypogonadism or genital abnormalities: Examination of the external genitalia in both sexes (cryptorchidism, short scrotum, micropenis, and low testicular volume in male and septate vagina, partial or complete vaginal atresia, absent vaginal and/or urethral orifices, persistent urogenital sinus)

- Hormone levels: from age of 13 years old starting checkup for testosterone (or estradiol+prolactin), gonadotropins FSH and LH, inhibin B

-Pelvic ultrasound examination (females). Complex genitourinary malformations can occur

5-insulin resistance/diabetes mellitus: fasting plasma glucose, HBA1C, fasting plasma Insulin annually and OGTT after age of 6 years old. Fasting plasma insulin concentration and hyperinsulinemia may be present from childhood.

6-Hypercholesterolemia: Yearly fasting lipid profile, including triglycerides

7-renal abnormality: 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).

- Yearly for symptoms(anemia, polyuria, and polydipsia), 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

8- Neuro-cognitive involvement: The baseline assessment includes careful neurological examination of the coordination and gait. An electroencephalogram should be performed for seizures.Brain MRI is requested for evaluation of other neurological conditions (ataxia, hypotonia, seizures)

Annual assessments for language (intelligible speech and sentence formation may be delayed until age four years), motor skills (gross and fine) and psychosocial skills.

9-Anosmia: Consider smell identification test (e.g. PSIT)

10-respiratory: Annual screening for sleep apnoea using a questionnaire; overnight oximetry if abnormal

11-Cardiology: The baseline evaluation involves auscultation of the heart, electrocardiogram and echocardiogram to assess for congenital heart defects and/or cardiomyopathy. If these conditions are present, the follow-up is recommended at the cardiologist’s indication. If the baseline evaluation is normal, re-evaluation is recommended only if symptoms appear. If there are

structural cardiac defects, antibiotic prophylaxis is recommended in case of surgical and dental procedures.

12-Hearing assessment: At diagnosis Audiogram / audiometry, tympanogram for Conductive and/or sensorineural hearing loss, then Yearly audiometry.

13-Hepatic disease: liver ultrasonography to evaluate a possible liver fibrosis and steatosis, measurements of plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gammaglutamyl transferase (GGT) level and tests for synthetic function (prothrombin time - PT, partial thromboplastin time -PTT). If these parameters are normal, they are reassessed annually.

14-Hypothyroidism: Thyroid function testing(TSH,FreeT4)at diagnosis, then annually

15- Dental abnormalities: assessment for hygiene, dental crowding and hypodontia. The follow-up is done every 6 months starting from the age of 1 year old.

16- ENT: Evaluation of the upper airways is important because laryngeal webs and bifid epiglottis can lead to life-threatening complications. Another rare abnormality that may be present is the choanal stenosis.

17-Genetic Testing: The best test to use is the gene panel containing the 26 genes involved in the BBS pathogenic mechanisms. If genetic testing is not available, it is recommended to initiate the management procedures if the clinical diagnostic criteria are met.

18-Craniofacial dysmorphism: consider anomalies including brachycephaly, macrocephaly, bitemporal narrowing, male frontal balding, large ears, short and narrow palpebral fissures, long shallow philtrum, nasal bridge hypoplasia, nasal shortening/reduced bulbosity at the nasal tip, relative upward displacement of the nose and upper lip, midfacial hypoplasia, and mild retrognathia

Table 2. base line and follow up monitoring:

Evaluation	Baseline	Follow up
Ophthalmologic	Electroretinogram, visual field testine, fundus exam,	Yearly
Orthopedic	Exam	---
Obesity	Weight, height, BMI, w/h ratio	Yearly
Hypogonadism	Exam, pelvic sono, From 13 years: testosterone, estradiol, prolactin, LH, FSH, inhibin B	From 13 years: testosterone, estradiol, prolactin, LH, FSH, inhibin B yearly
Diabetes Mellitus	FBS, HBA1C, fasting plasma insulin, OGTT (from 6 year)	FBS, HBA1C, fasting plasma insulin, OGTT (from 6 year) yearly
Hypercholesterolemia	TG, CHOL, LDL, HDL	TG, CHOL, LDL, HDL (yearly)
Renal	Urea, Cr, electrolyte, GFR, UA, Urine albumin/Cr, BP, 24 h BP monitoring	Urea, Cr, electrolyte, GFR, UA, Urine albumin/Cr, BP, 24 h BP monitoring (yearly)
neurology	EEG, Exam	Yearly exam
Respiratory	Questionnaire for sleep apnea	Questionnaire for sleep apnea (yearly)
Cardiology	Auscultation, ECG, echo	---
Hearing	Audiometry, tympanogram	Audiometry (yearly)
Hepatic	Sono, ALT, AST, GGT, PT, PTT	Sono, ALT, AST, GGT, PT, PTT (yearly)
Hypothyroidism	TSH, Free T4	TSH, Free T4 (yearly)
Dental	Exam from 1 year	Every 6 months
ENT	Exam	---