BARDET BIEDL SYNDROME WITH TYPICAL RETINITIS PIGMENTOSA AND HYPERGONADOTROPHIC HYPOGONADISM

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Abstract

Bardet Biedl syndrome (BBS) is a rare autosomal recessive disease, characterized by clinical and genetic heterogeneity. Many genes are involved. BBS seems to be different from Lawrence Moon BBS, although they share some clinical symptoms. The main clinical signs are obesity, pigmentary retinopathy, kidney malformations, and hypogenitalism.

Our aim is to report a case with typical retinis pigmentosa, hypergonadotrophic hypogonadism and cerebellum cyst.

Case report. A man aged 18 was referred for obesity and blindness. His family history was marked by obesity and diabetes mellitus type II. His medical history began very soon, as he was born with polydactyly, then he became obese and had difficulty to learn and to see. His blindness was progressive, and his puberty was delayed. Clinical and biological exams showed: severe android obesity (BMI = 40kg/m², waist circumference = 130cm), pigmentary retinopathy, small testes with high FSH = 17 mU/mL (1-8), and normal LH = 6.13 mU/mL (0.6-12), empty sellae, cerebellum cyst, renal malformations, and signs of chronic infections. He did not have any spasticity or ataxia. Genetic study was not done.

Conclusion. In this case, all features argued for typical BBS, except for testicular insufficiency which is classically described as hypogonadotrophic. Infections should be treated vigorously to avoid renal insufficiency.

Key words: Bardet Biedl syndrome, retinis pigmentosa, obesity, hypogonadism, arachnoid cyst, hydronephrosis.

INTRODUCTION

Bardet–Biedl syndrome (BBS), a form of Laurence–Moon–Biedl syndrome for some authors (1), or different for others, although they share many features, is a very rare inherited disease due to mutations in at least fourteen genes: BBS1 to BBS14 (2). It is an autosomal recessive disease, so only homozygous are symptomatic. The main features or cardinal signs are obesity, severe retinal dystrophy, kidney malformations, and abnormal extremities, plus hypogonadism especially for men (1, 3). Other signs are learning disability, strabismus, cataracts, diabetes mellitus, cerebral (4) or bone (5) abnormalities, and dental malformations (6).
Our aim is to report a young man with typical retinis pigmentosa, numerous malformations, hypogenitalism due to primary testicular insufficiency and cerebellum arachnoid cyst.

**CASE REPORT**

A young man aged 18 was referred to our department for obesity and blindness. His family history was unremarkable except for consanguinity (his parents are first cousins), obesity and diabetes mellitus type II. His medical history began soon as he was born with abnormal feet and hands. Then he was operated on for polydactyly of both hands. He became obese quickly and had difficulty to learn and see in the dark. His visual loss was progressive and at the age of ten he was totally blind. His puberty was delayed.

Clinical exam showed a blind hypogonadic man with severe android obesity (BMI: 40kg/m², waist circumference: 106cm), left genu valgum, and abnormal feet with polydactyly (Fig 1). On his hands there were scars of surgery for polydactyly. Neurological exam was normal. Heart function was normal too. Blood pressure was equal to 120/40mm mercury and heart frequency was equal to 70 beats/min.

There were all features of hypogonadism (Fig.1) such as gynecomastia without galactorrhea, small penis and testicles, and impaired growth of body hair (Fig.2).

Ophthalmological exam showed typical retinis pigmentosa with optic atrophy (Fig.3)

Echocardiography was normal, but for pulmonary function there was a restrictive ventilatory syndrome.

Hormonal exams (Table I) were normal for thyroid and adrenal functions, but there was a primary testicular insufficiency. Somatotrope axis was not explored as there were no signs of somatotrophic deficit and obesity is known to reduce growth hormone response to hypoglycaemia test.

**Figure 1.** Clinical and radiological features: android obesity, genu valgum, abnormal feet and polydactyly.
Pelvis echosonography confirmed small testes as the right one measured 32x17mm and the left one 31x17mm (Fig.2). The pelvic scan showed prostatic calcifications, hydronephrosis of the right kidney and foetal lobulations in the left one (Fig.4).

Cerebral MRI demonstrated three abnormalities: maxillary sinusitis (Fig.5a), retro cerebellum arachnoid cyst (Fig.5b), and pituitary empty sella (Fig.5c).

Biological exams were unremarkable except for hypertriglyceridemia (2.52g/L, n<1.5) and hypercholesterolemia (2.52g/L n<2g), with normal glucose metabolism (fasting glycaemia: 0.87g/L, and glycaemia after glucose loading = 1.34g/L). For kidney function: urea was equal to 0.31g/L (0.10-0.55), creatinine = 18.1mg/L (4-12) and creatinine clearance was slightly decreased: 86.23mL/min (Normal >97-137mL/mn/1.73m²). Hepatic function was normal.

In this observation, Bardet-Biedl syndrome was considered. Furthermore, retinal examinations revealed typical features of retinitis pigmentosa and optic atrophy.

Figure 2. Hypogonadism features: gynecomastia, small penis and testes, lack of beard and reduced male hair distribution.

Figure 3. Typical retinitis pigmentosa (RP) and optic atrophy (OA).
syndrome diagnosis was evident as all major criteria were present such as: typical retinal dystrophy, severe obesity and postaxial polydactyly, learning disability, hypogonadism and kidney malformations. Some minor criteria were also present such as pubertal delay and clumsiness. Other signs such as speech disorder, hearing loss, polyuria, polydipsia and diabetes mellitus, poor coordination, spasticity, cardiac abnormalities and hepatic fibrosis were

<table>
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<th>FSH (mU/mL)</th>
<th>LH (mU/mL)</th>
<th>FT4 (pmol/L)</th>
<th>TSH (µU/mL)</th>
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<td>6.13</td>
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<td>1-8</td>
<td>0.6-12</td>
<td>8-24.5</td>
<td>0.2-4</td>
<td>154-638</td>
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</table>

Figure 4 showing damaged kidneys.

Figure 5. Brain MRI showing: maxillary sinusitis (a), retro cerebellum archnoid cyst (b), and empty sella (c).
The prognosis of this patient was considered poor as he was already blind and had severe obesity and kidney alteration due to congenital malformations worsened probably by chronic infections.

**DISCUSSION**

Bardet-Biedl syndrome (BBS) is a pleiotropic disorder with multiple anomalies that are inherited in an autosomal recessive pattern (7). It is due to mutations of at least 14 genes (2, 7), but the most common seems to be BBS1. BBS is commonly found in communities with high consanguinity (8,9). BBS does not seem to be very different from Lawrence Moon Bardet-Biedl syndrome or LMBBS (1,8,10) as both are phenotypically and genetically heterogeneous and known to be under BBS9 gene control (2). BBS and LMBBS diagnoses are established by clinical findings combining major and minor signs (1).

BBS affects boys and girls, but it is usually more severe in males (1). Characteristic features are severe retinal dystrophy, abnormal feet and hands, obesity, renal abnormalities, and hypogonitalism (especially in men). Mental retardation, polydactyly, total or partial syndactyly (3) are usually absent in female cases (1). Heart abnormalities such as cardiac malformations, cardiomyopathy of unknown etiology and left septum hypertrophy absent in our case are reported in 50% by Albedour (12). It seems that BBS genes implicated in cilia functions are involved in regulation of heart endothelium and vascular function. So, disruption in BBS2 and BBS6 genes affects differently the vascular function (13).

Pulmonary problems due to ciliary dysfunction (11,12) and/or to obesity may be observed as in our case.

Major and preoccupant problems are retinal dystrophy and kidney abnormalities. Retinal dystrophy also called rod-cone dystrophy leading to blindness is present in 90 to 100% (14, 15) especially when the electroretinogram is systematically done, but typical retinal dystrophy, also called retinis pigmentosa, as observed in our case and in Andrade’s (14) is exceptional. Its prognosis is very poor as there is still no preventive or curative treatment.

Other ophthalmological abnormalities are strabismus, cataracts, and astigmatism (23).

The second important problem is represented by kidney abnormalities. The numerous congenital malformations of the urinary tract and kidneys added to frequent infections lead to renal insufficiency. So, renal transplantation is more precocious in BBS than in other diseases. For Sharifian (16) mean age at renal transplantation in BBS is eleven years old. The prognosis is poor, especially in patients with congenital malformations, chronic infections and cardiovascular risk factors, such as severe obesity, high blood pressure (10), dyslipidemia (as in our case) and diabetes mellitus (17). Hypogonadism, and renal osteo-dystrophia increase bone deformities, osteoporosis and fracture risk (5,18).

Obesity and metabolic syndrome (19) are apparently due to leptine
resistance (20,21), and are probably worsened by sedentary and ortho-paedic problems such as scoliosis and tibia valga or vara (22).

Other abnormalities connected to the malformative syndrome are numerous (23), among them gingival overgrowth and dental abnormalities (including hypodontia, microdentia, shorts roots and deep plate) are reported by Drugowick (6).

Apart from hearing loss, neurological symptoms are unusual (24), but systematic brain MRI can show a lot of abnormalities (4, 24, 25) such as cerebellar vermis hypoplasia, mega cisterna magna (24), reduction in total grey matter volume, hippocampal volume loss, ventriculomegaly and other lesions (25). In our patient, we discovered a cerebellum arachnoid cyst (rarely reported in literature), a maxillary sinusitis, and an empty sella without any pituitary deficit. The empty sella is also reported by others (26, 27). Guran (28) also pointed to pituitary abnormalities such as pituitary hypoplasia; rathke cleft cyst, and tumors. These pathological findings may be responsible for hormonal disturbances such as growth hormone deficiency, hyper prolactinemia, hypogonadotrophic hypogonadism, and central precocious puberty.

Gonadal abnormalities are among major signs. In males, hypogonadotrophic hypogonadism seems to be more frequent leading to small penile shaft and small testes with or without cryptorchidism and hypospadias (23). Hypergonadotrophic hypogonadism (as observed in our patient) is rarer. It may result from ciliopathy and/or recurrent infections.

In females many abnormalities have been observed such as hypoplastic ovaries, uterus and fallopian tubes. Total or partial vaginal atresia is also possible. Persistent urogenital sinus, lack of vaginal or urethral orifice, hydrometrocolpos, and vesico-vaginal fistula are also reported (23).

Tumor development is more frequent in BBS (or their relatives) than in normal subjects. A high frequency is observed especially for transplanted patients (29). Reported tumors are lymphoma (29), glioma (30), cranio-pharyngioma (31) and renal carcinoma (8, 32, 33).

Functional prognosis is very poor because of motor and visual handicaps. Vital prognosis is dominated by renal insufficiency and metabolic syndrome. These complications may be delayed if there is a precocious or prenatal diagnosis (using second-trimester ultrasound examination to detect some abnormalities such as post axial polydactyly, renal cysts and other malformations) and a multidisciplinary approach.

In conclusion, Bardet Biedl syndrome is a very rare inherited disease caused by several genes mutations. At least fourteen are known (BBS1-14). BBS9 is involved in ciliary diseases too, which explains their association to the described syndrome. The diagnosis is classically based on clinical features classified as major and minor. Among major signs retinal dystrophy, renal malformations and severe obesity are responsible for the very poor prognosis. A multidisciplinary approach of this syndrome is more than necessary as orthopedic treatment is needed to correct
severe deformities, diet and some symptomatic treatment may help to decrease cardiovascular risk. Regular checking for tumor development is recommended, and vigorous treatment for urinary infections may prevent rapid renal destruction as end-stage renal failure is the most frequent cause of death in BBS.

Nowadays, the best way to prevent this syndrome is represented by genetic and psychological counseling in order to avoid interfamily marriages, as molecular diagnosis is possible only in informative families where there is already one case with molecular confirmed diagnosis.

Declaration of interest
The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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