*Case Report*

# BARDET-BIEDL SYNDROME

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## ABSTRACT

A 3,5-year-old boy was admitted with febrile convulsion and bronchitis. He had polydactyly, obesity, and micropenis on his physical examination which indicated the Bardet Biedl syndrome. Then further investigations were made to make the definitive diagnosis, in the light of literature. We would like to present this case report.

**Key Words:** Bardet Biedl syndrome, Obesity, Retinitis pigmentosa, Hypogonadism, Mental retardation, Polydactyly.

## INTRODUCTION

Bardet Biedl syndrome is an autosomal recessively inherited genetic disorder characterized by retinitis pigmentosa, obesity, mental retardation, hypogonadism and polydactyly. The five findings together are called "the pentad" and are found in about 28 - 47.5% of cases. In the remaining cases clinical findings are incomplete.

Urogenital anomalies are also frequently seen. During advancing ages renal failure, blindness occur. Therefore proper diagnosis and genetic consultation are important. Our purpose in the paper was to discuss Bardet Biedl syndrome and its features. Therefore, we present a Bardet Biedl case diagnosed in our clinic.

## CASE REPORT

A 3,5-year-old boy was presented with febrile convulsion and bronchitis. He is the second child of a healthy couple, both 30 years of age. He was delivered by normal spontaneous delivery with a birth weight of 3350 grams. The first child of the family is 10 years of age and healthy.

Our patient had 7 fingers on his right hand and 6 fingers on his left hand, 6 toes on his left and right feet, at birth. Up to 1 year of age he was breast fed. He was able to sit without support at 6 months and to walk after the first year. He started to speak when he was 2 years old (he still does not speak properly). From three months of age he had recurrent bronchitis attacks and was hospitalized due to bronchopneumonia at seventh months of age. A year ago he had two febrile convulsions with a one week interval and a third one just before admission to our clinic.

Physical Examination: His axillary temperature was 38,5 °C and he had dyspnea. His height: 99 cm (50th percentile), weight: 25 kg (over 97th percentile), head circumference: 50 cm (90th percentile). Heart rate was 132/min and had no pathologic heart sounds. The liver and the spleen were nonpalpable. There were 7 fingers

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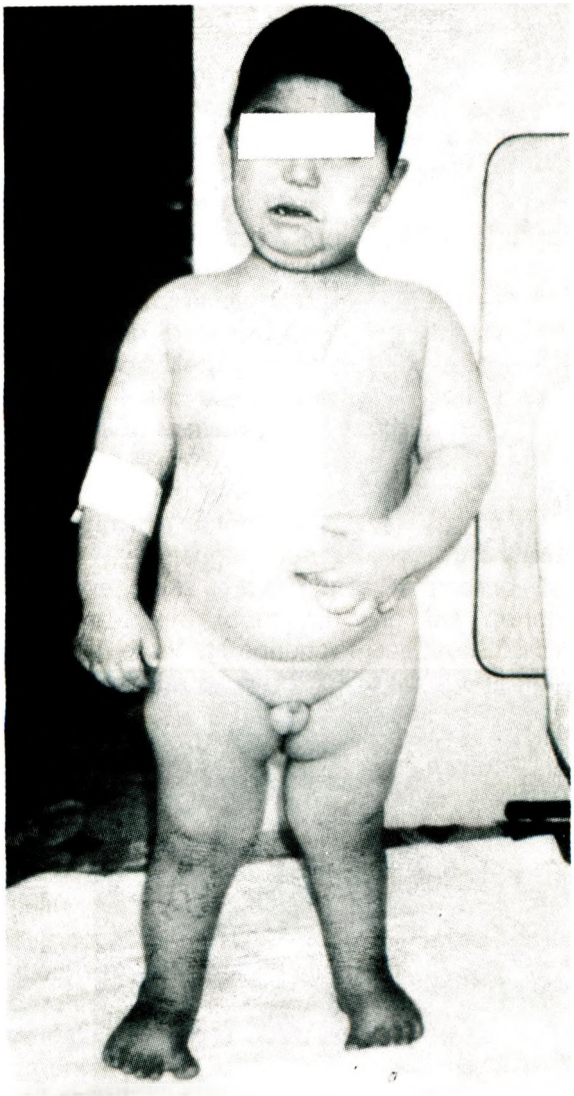

**Fig.1.:** Frontal view of the patient

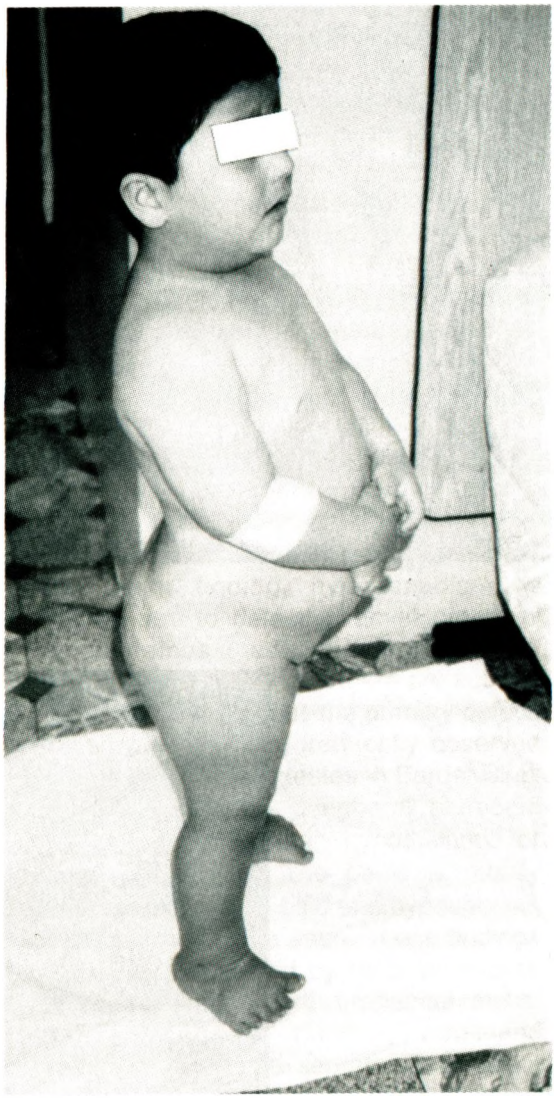

**Fig.2.:** Lateral view of the patient

on the right hand, 6 on the left hand and 6 toes on his right foot. The sixth toe on the left foot which was present at birth, was excised by an operation. An operation scar was observed beneath the 5th digit of the left foot. Phenotipically he was a male, with the penile length of 3 cm. (Normal penile length for a 3-4 year old male is 5.5 ± 0.9 cm.) His testes were bilaterally descended.

Laboratory Findings: On laboratory investigation, his blood count was normal as well as his blood biochemistry. C reactive protein was positive. Anti streptolysin O was normal. Erythrocyte sedimentation rate was normal. PPD was negative. P-A chest roentgenogram was normal. Urine sampling was normal.

On the right hand and wrist graphies; the fifth metacarpal bone was observed wide and deformed. The fifth phalanx and two additional fingers originated from this metacarpal bone. The one in the middle of the additional fingers had proximal, middle and distal phalangeal bones, whereas the other two had only two phalanxes each. No osseous syndactyly was observed. On the left hand there was only one additional finger originating from the

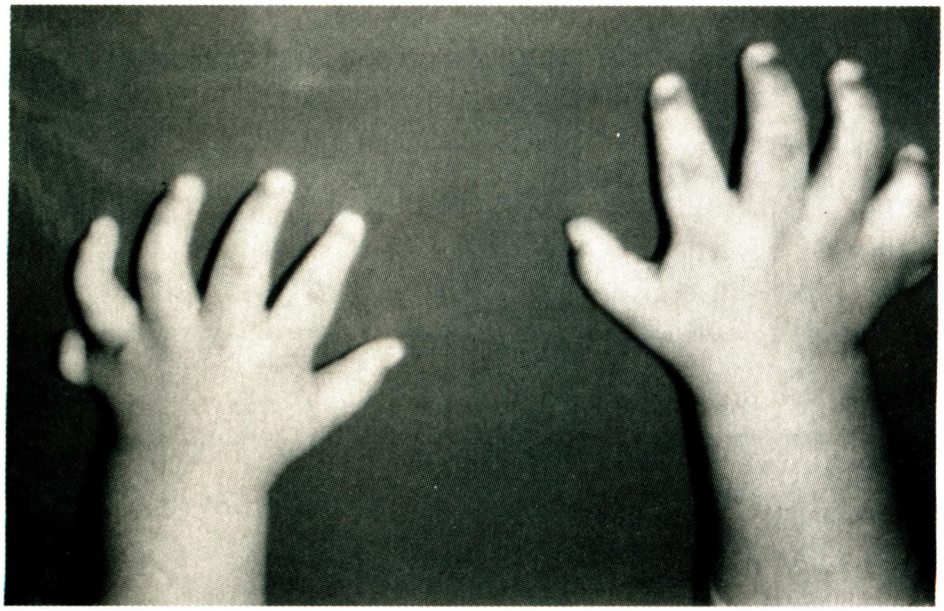

**Fig.3.:** Both hands of the patient

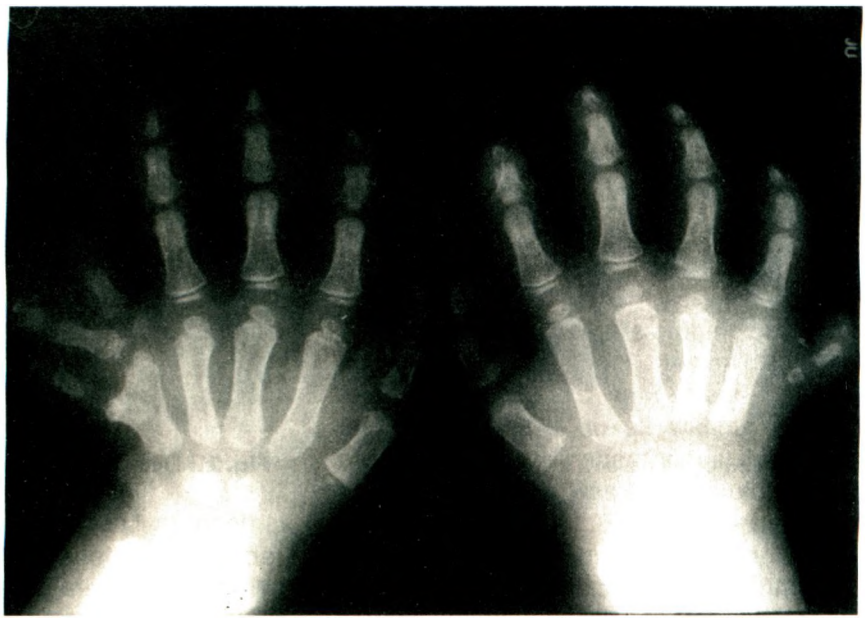

**Fig.4.:** X-Ray view of the hands

lateral side of the hand, with no osseous connection to the metacarps or phalangeal bones. The bone age of the patient was 3 years. On the right foot and ankle roentgenogram, an additional toe originating from the fifth metatarsal bone with a proximal and a distal phalanx was observed. There was no osseous syndactyly. The pelvic and sella graphies were normal.

Electroencephalograph, computed cranial tomography, abdominal ultrasonography and echocardiography results of the patient were normal. His IQ was at the level of 3 years of age. The ophthalmoscopic examination revealed a normal papilla and peripheral retina; however there was a dysmorphic figure in the macula, which was a centrally located hypopigmented semi-discus area. It was accepted as a central form of retinitis pigmentosa.

## DISCUSSION

Bardet Biedl syndrome is an autosomal recessively inherited genetic disorder characterized by retinitis pigmentosa, obesity, mental retardation, hypogonadism and polydactyly. Among the features of this syndrome polydactyly is the most common one and noticed at birth. Obesity, hypogonadism, mental retardation and ocular findings appear later and can be seen in varied forms. The five findings together are called "the pentad", and are found in about 28 - 47.5% of cases. In the remaining cases clinical findings are incomplete (1-4).

The heterogenecity and variability of the clinical findings in this autosomal recessively inherited disease were thought to be caused by more than one gene locus. Four genes related to this syndrome were identified with the genetic studies. In order of frequency these are: BBS1 at 11q13; BBS2 at 16q21; BBS4 at 15q22; BBS3 at 3p12 (5,6). In our case only the karyotype was determined which was 46, XY. No molecular genetic investigation could be performed.

The ocular findings vary in a spectrum from normal to anophthalmia. The classical form is retinitis pigmentosa. Histologically the number of rods, cones and ganglion cells in the outer nuclear layer of the retina is decreased. Around the retinal vessels of ganglionic cell layer, a pigment collection is observed. Although retinitis pigmentosa is the typical anomaly of the syndrome; atypical retinal alterations, apigmented retinitis can be seen as well. In our case; a dysmorphic figure, a centrally located hypopigmented semi-discus area, was seen in macula. It was regarded as the central form of retinitis pigmentosa. It is mentioned that ocular findings start in early childhood (around 3-4 years of age) in this syndrome and the visual acuity decreases progressively. The fundal signs are atypical and variable (3,4,7). Optic atrophy, cataract, myopia and external ophthalmoplegia are among the atypical ocular findings of Bardet Biedl syndrome (1,2).

Obesity starts to appear around 4 years of age. It can also be observed in earlier ages, even at birth. Our patient had normal birth weight, and was around 10 kg at 6 months. The weight at hospitalization was 25 kg (over 97th percentile) and the body mass index was 25.2 (over 97th percentile). In patients with Bardet Biedl syndrome obesity is located on the trunk, thighs and pelvis and sometimes on the face. The obesity of our patient was compatible with this type of distribution. This type of obesity can be misdiagnosed as benign adolescent obesity in which height is normal and is more frequently seen after 8 years of age. But in this syndrome, obesity starts earlier, height is shorter and can even be regarded as dwarfism. Rarely the patients can be tall. The height of our patient was unaffected (99 cm, 50th percentile). But the height can be retarded within years due to the effect of the syndrome. Obesity and height were thought to be related with the responsible gene loci. (5,6)

The third major finding, hypogonadism, is thought to be due to defective development of the hypothalamus according to many researchers. On the other hand there are authors indicating germinal aplasia as the primary defect. Accoding to those authors, frequently observed undescended and atrophic testes in Bardet Biedl syndrome are related to peripheral hormonal unresponsiveness rather than hypothalamic or hypopyseal sequela (8). The penis is mostly small. The scrotum can be bifid and hypospodias or prostatic urethra can be seen. These findings are frequently accompanied by renal anomalies (1,2). In females, persistent urogenital sinus, ectopic uretra, hypoplasia of uterus, ovaries and tubes, vaginal atresia and septation can occur (9). In our patient the distance from the tip of the penis to the symphisis pubis was 3 cm (micropenis) (The normal penile length in this age group is 5.5 ± 0.9 cm.). The FSH level was 0.508 mIU / ml (<1-3 IU/ml), LH level was < 0.1 mIU/ml (<1-4 mIU /ml).

Some authors defend that mental retardation, obesity, diabetes inspidus and gonadal hypofunction are related to hypothalamic defects, whereas some others reject this relation (1,2). In our patient, the sella graphy and the cranial tomography were found to be normal.

The fourth finding in the pentad, mental retardation, is observed in 87 % of cases. In most cases mental retardation becomes evident at school age and progresses together with ocular findings. Serious mental defects and (rarely)

psychosis can be seen (1,2). The intelligence level of our patient was around 3 years of age.

The last finding of the pentad, polydactyly, is generally present from birth, so it is very important in indicating Bardet Biedl syndrome. In any patient presenting with visual defects and obesity, or amputated additional finger or any anomaly in the extremities, the diagnosis may be missed. Other finger anomalies that can be seen in Bardet Biedl syndrome are syndactyly, polydactyly, hexadactyly which are usually post-axial. Sometimes an additional thumb or duplication of the other fingers can be seen. If not all extremities are affected, polydactyly is seen more in feet. In some cases without polydactyly, radiological findings such as short and wide metacarpal bones with flattening of their articular surfaces, longer or shorter ulna can be found (10). The other anomalies of the skeletal system are microcephaly, acrocephaly and craniosynostosis. Perthes Calve Legg, genu valgum, foot deformities and tooth anomalies have rarely been reported. Our patient had polydactyly affecting all extremities. The additional toe on the left foot had been excised.

Some anomalies can accompany typical findings. These are cardiac anomalies such as atrioventricular septal defect, PDA, pulmonary stenosis, hypoplastic aorta, transposition of the great arteries, single ventricle and dextrocardia. Interventricular septal hypertrophy and dilated cardiomyopathy are diagnosed by echocardiograhy (11). The echocardiography of our patient was normal.

Urogenital system anomalies are also frequently seen and should especially be paid attention to. Penile anomalies accompanied by urethral anomalies should warn us about underlying renal anomalies. Cystic kidney dysplasia, urethral stenosis, hydronephrosis, vesicourethral reflux, vesicovaginal fistula and urethral sinus may occur. Chronic renal failure develops in terminal patients. Therefore, all cases with or without renal symptoms should be searched for renal anomalies. In the early diagnosis renal scintigraphy has been shown to be helpful (3, 12-14). In our case urinalysis, urine culture and renal ultrasonography were all normal. Renal scintigraphy could not be performed.

Rarely anomalies like anal agenesis or Hirschsprung's disease have been reported. We made the diagnosis on the basis of polydactyly, obesity, retinal changes in macula and micropenis. Mental retardation could not clearly be evaluated but is expected to show up during school-age.

In some cases iron deficiency anemia has been reported, which was not present in our patient. Whether anemia is a part of the syndrome or simply the iron deficiency anemia of childhood, cannot be clearly decided in the absence of other specific findings (15).

Our patient has had three simple febrile convulsions. Cases with convulsion have been reported in the related papers. (16) EEG of our patient was reported as normal.

Our patient was referred to a university hospital for further genetic evaluation and analysis. He was called for a follow up in order to discover possible visual disorders and renal involvement of the disease in time.

It is difficult to make the diagnosis of Bardet Biedl syndrome. Therefore attention should be paid on physical examination and evaluation of analyses. Polydactyly is one of the major symptoms to arouse suspicion. When it is absent, radiological investigations for other osseous abnormalities can lead to diagnosis. The syndrome should be considered among the reasons of childhood obesity. Making the diagnosis of the syndrome will help the early diagnosis of accompanying ocular, renal and cardiac anomalies. In heterozygote cases, obesity and abnormalities in height have been reported, thus family screening is important.

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