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# POLYDACTYLY AND OBESITY – THE CLINICAL MANIFESTATION OF CILIOPATHY: A BOY WITH BARDET-BIEDL SYNDROME

## POLIDAKTYLIA I OTYŁOŚĆ JAKO MANIFESTACJA KLINICZNA CILIOPATII: CHŁOPIEC Z ZESPOŁEM BARDET-BIEDLA

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**Abstract**

*The prevalence of obesity in children is still rising all over the world. The most common reason for significant weight gain is a high-calorie diet and decreased physical activity. However, apart from environmental factors, genetic predisposition plays a crucial role in the pathomechanism of obesity. We present the case of a boy with pathological obesity and Bardet-Biedl syndrome (BBS). BBS is a ciliopathy, a heterogeneous group of rare disorders associated with defects in primary cilia. Other clinical signs and symptoms of BBS are: polydactyly, hypertension, hyperlipidemia, hypogonadotrophic hypogonadism, intellectual disability, rod-cone dystrophy, genitourinary and renal abnormalities. Conclusions: genetic factors of rapid weight gain should be taken into consideration in a child with obesity. Polydactyly can be associated with ciliopathy. A patient with Bardet-Biedl syndrome requires multi-specialist care.*

**Key words:** polydactyly, obesity, retinitis pigmentosa, dysplastic kidney, ciliopathy

**Streszczenie**

*Częstość występowania otyłości u dzieci stale wzrasta. Najczęstszą przyczyną zbyt dużego przyrostu masy ciała jest nadmierna podaż kalorii i brak aktywności fizycznej. Jednak oprócz czynników środowiskowych należy zawsze pamiętać o roli czynników genetycznych w powstawaniu otyłości. Przedstawiamy przypadek pacjenta, u którego patologiczna otyłość była objawem zespołu Bardeta-Biedla – rzadkiej choroby uwarunkowanej genetycznie. BBS należy do ciliopatii – grupy chorób związanych z defektem rzęski pierwotnej. Innymi objawami zespołu Bardeta-Biedla są: polidaktylia, nadciśnienie tętnicze, hiperlipidemia, hipogonadyzm hipogonadotropowy, niesprawność intelektualna, zwyrodnienie barwnikowe siatkówki, wady nerek i układu moczowo-płciowego.*
*Wnioski: W przypadku szybkiego przyrostu masy ciała u dzieci w procesie różnicowania należy brać pod uwagę czynniki genetyczne otyłości. Polidaktylia może występować u pacjentów z ciliopatią. Pacjent z BBS wymaga opieki wielospecjalistycznej.*

**Słowa kluczowe:** polidaktylia, otyłość, zwyrodnienie barwnikowe siatkówki, nerka dyspalstyczna, ciliopatia

## INTRODUCTION

The prevalence of obesity in children is still rising in many countries. Taking into consideration that the reason for overweight and obesity can be connected with environmental as well as genetic factors, the problem is extremely important for pediatricians in diagnostic processes [1]. Polydactyly is a congenital abnormality involving the presence of extra digits with the incidence of 0.3-1.3 per 1000 live births in the white population and 3.6-139 per 1000 live births among black people [2]. Polydactyly can be unilateral or bilateral; preaxial or postaxial. Postaxial polydactyly is associated with an extra digit on the ulnar or the fibular side of the limb; preaxial with an extra digit on the radial or tibial side of the limb. About 15% of newborns with polydactyly have other congenital abnormalities. In most patients polydactyly occurs as an isolated anomaly of unknown etiology, but in some children it can be syndromal.

## CASE REPORT

A one-year-old boy was admitted to the Pediatric Nephrology Department because of obesity, polydactyly and dysplastic kidneys. The child was born at term, his birth weight was 3660 g and Apgar score was 9 points. He was breast-fed for the first 2 months, then he received a milk formula. His mother started introducing fruit, vegetables and meat into his diet from the age of 6 months. A significant weight gain was observed during his first year of life: at 6 months he weighed 8240 g, at 11 months 14.560 g (>95th percentile). On physical examination, several abnormalities were noted, including: obesity with the weight of 14.9 kg (>95$^{th}$ pecentile), height – 78.5 cm (>95th percentile), BMI – 24.0 kg/m$^2$ (+5.2SDS), also postaxial polydactyly of hands and feet (24 fingers) and small-volume testes. Blood pressure was normal: 94/58 mmHg. The laboratory blood test showed the normal function of the liver, kidneys and thyroid gland. Urine specific gravity was <1005. Blood level of FSH, LH and testosterone level were decreased. Abdominal ultrasound revealed dysplastic kidneys. The ultrasound of the scrotum showed the small volume of testes (0.24 ml, 0.3 ml). Echocardiography was normal. Ophtalmoscopic examination revealed increased retinal pigment collections (early stages of retinitis pigmentosa). X-ray examination of feet and hands were performed before the surgical removal of the accessory digits (fig. 1, 2). Both parents have normal hands and feet and no known congenital abnormalities. Because of obesity, polydactyly, dysplastic kidneys and hypogonadism, we sent the blood samples for genetic tests. Karyotype was normal 46, XY. Molecular analysis was performed in a DNA sample isolated from blood – 347 mutations in 16 genes associated with Bardet-Biedl syndrome were checked and p.Ser479X mutation (in one allele of *MKKS* the (*BBS6*) gene was found. (APEX v.5.0 method). The mutation was also confirmed by Sanger sequencing. This type of mutation in the *MKKS* gene is present in the registry of mutations (HGMD) and correlates with BBS.

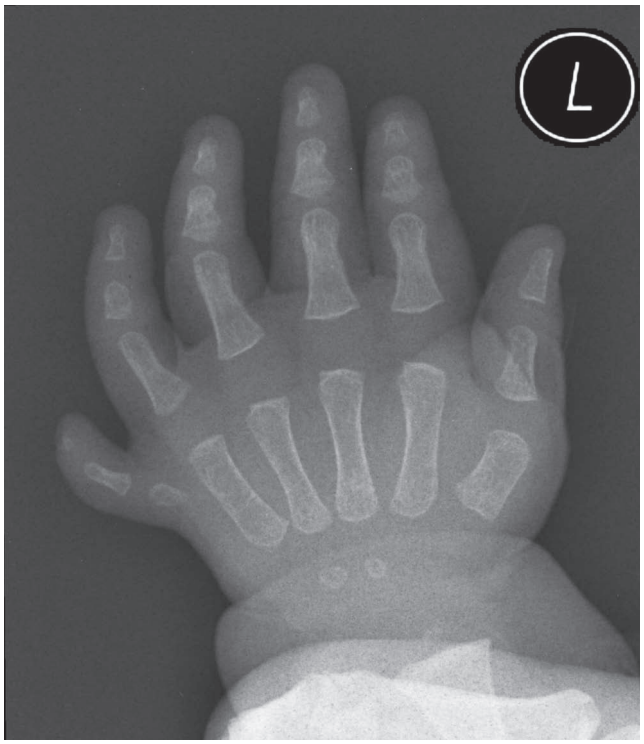


Fig. 1. X – ray of the left hand with an extra digit.

*Ryc. 1. Zdjęcie RTG lewej dłoni z dodatkowym palcem.*

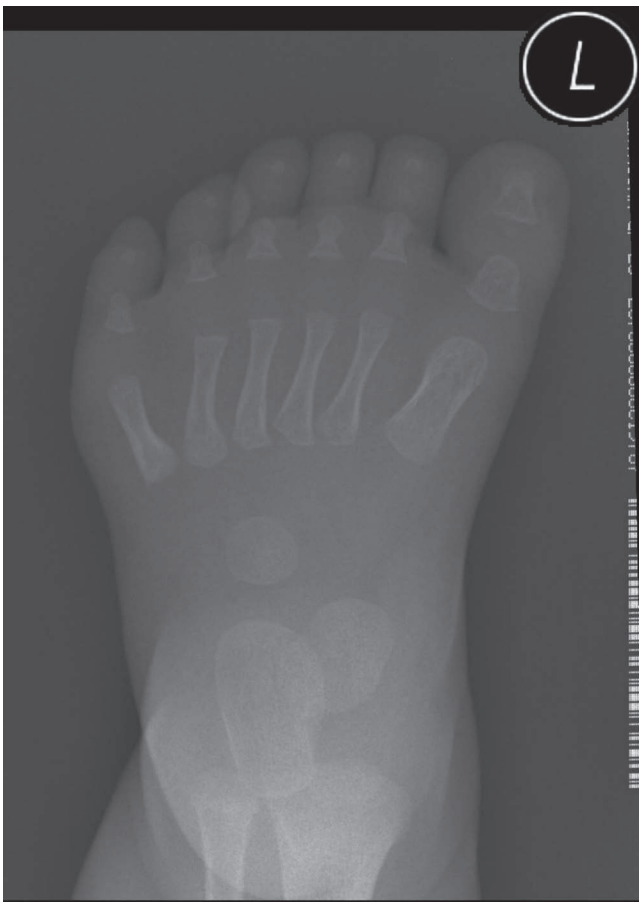


Fig. 2. X – ray of the left foot with an extra digit.

*Ryc. 2. Zdjęcie RTG lewej stopy z dodatkowym palcem.*

Table I. Clinical manifestation of Bardet-Biedl syndrome.
*Tabela I. Objawy kliniczne zespołu Bardeta-Biedla.*

| | **Frequency** ***Częstość*** | **Characteristics of changes** ***Zmiany charakterystyczne*** |
|---|---|---|
| Obesity *Otyłość* | 72-92% | Truncal obesity *Otyłość centralna* |
| Polydactyly, brachydactyly/syndactyly *Polidaktylia, brachydaktylia, syndaktylia* | 68-81% | Postaxial polydactyly *Polidaktylia pozaosiowa* |
| Rod-cone dystrophy *Dystrofia czopkowo-pręcikowa* | 90% | Night blindness *Ślepota nocna* |
| Renal anomalies *Wady nerek* | 53-82% | Renal dysplasia, FSGS *Dysplazja nerek, ogniskowe segmentalne stwardnienie kłębuszków nerkowych* |
| Genital abnormalities *Wady narządów płciowych* | 59% | Hypogonadism, cryptorchidism, abnormalities of the vagina, uterus, ovaries and fallopian tubes *Hipogonadyzm, wnętrostwo, wady pochwy, macicy i jajowodów* |
| Cardiovascular anomalies *Wady układu krążenia* | ~50% | Aortic stenosis, patent ductus arteriosis, cardiomyopathy *Stenoza aortalna, przetrwały przewód tętniczy, kardiomiopatia* |
| Behavioral abnormalities *Zaburzenia zachowania* | ~30% | Emotional immaturity, depression *Niedojrzałość emocjonalna, depresja* |
| Speech delay *Opóźniony rozwój mowy* | | Incoordination of the pharyngeal/laryngeal muscles *Zaburzenia koordnacji mięśni krtani i gardła* |
| Developmental delay *Opóźnienie rozwoju psychoruchowego* | | Delayed developmental milestones, learning disabilities *Opóźniony rozwój pcychomotoryczny, trudności w nauce* |
| Ataxia *Ataksja* | | Poor coordination, imbalance *Zaburzenia koordynacji i równowagi* |
| Diabetes mellitus *Cukrzyca* | ~6% | Type 2 *Typ 2* |
| Orodental abnormalities *Wady zębów i zgryzu* | | Dental crowding, hypodontia *Stłoczenie zębów, brak zawiązków zębowych* |
| Hepatic involvement *Choroby wątroby* | | Biliary fibrosis, portal hypertension *Włóknienie, nadciśnienie wrotne* |
| Craniofacial dysmorphism *Wady czaszki i twarzy* | | Brachycephaly, macrocephaly, large ears, depressed nasal bridge, short nose, narrow forehead *Brachycefalia, makrocefalia, duże uszy, płaska nasada nosa, wąskie czoło* |
| Other *Inne* | | Anosmia, eye abnormalities (strabismus, cataract, astigmatism), hypertonia, Hirschprung disease *Anosmia, zez, zaćma, astygmatyzm, wzmożone napięcie mięśniowe, choroba Hirschprunga* |

## DISCUSSION

Differential diagnosis of obesity in children includes genetic diseases. Physical examination can be helpful in finding congenital abnormalities and establishing the diagnosis. A broad range of symptoms, such as polydactyly, cystic kidney disease, cardiac defects, skeletal abnormalities, defects of the central nervous system, eye changes can be seen in ciliopathies. They are a heterogeneous group of disorders associated with defects in primary cilia or intraflagellar transport. Ciliary

defects have been noted in: Bardet-Biedl syndrome (BBS), autosomal dominant and recessive polycystic kidney disease (ADPKD, ARPKD), nephronophtisis (NPHP), Joubert syndrome (JBTS), Senior-Loken syndrome (SLS), orofaciodigital syndrome (OFD), Jeune syndrome, Leber congenital amaurosis (LCA), Meckel-Gruber syndrome (MKS), Usher syndrome (US) and retinal dystrophy (RD). For each of these diseases significant phenotypic variability has been observed among members of the same family. Some ciliopatithies have special clinical features. For example MKS is a lethal disease, JBTS is characterized by radiological findings in the central nervous system known as the molar tooth sign. In our patient, the most probable diagnosis was BBS with a clinical triad: obesity, polydactyly and retinopathy. Rod-cone dystrophy and obesity is also observed in Alstrom syndrome associated with mutations in ALMS1, but in contrast to BBS in Alstrom syndrome we do not observe polydactyly. Although the mutation was identified only in one allele of the *MKKS* gene, it does not exclude the clinical diagnosis of Bardet – Biedl syndrome in our patient. However, further studies to find a mutation on the second allele are indicated for the full molecular verification of the clinical diagnosis of BBS in the proband. It is possible that mutation on the second allele occurs less frequently and therefore was not included in the diagnostic panel of mutations. Nevertheless, in some families, clinical phenotype of BBS may be caused by pathogenic mutations in more than one BBS locus. Full molecular verification of the clinical diagnosis of BBS (identification of the pathogenic mutation on both alleles) provides the grounds for genetic counselling.

Mutations of the *MKKS* can also cause McKusick-Kaufman syndrome (MKS), which include such congenital abnormalities as hydrometrocolpos, postaxial polydactyly and congenital heart disease

Bardet-Biedl syndrome (BBS, MIM 209900) is in most cases inherited in an autosomal recessive manner. So far eighteen genes are associated with BBS and include: *$BBS_1$, $BBS_2$, ARL6 ($BBS_3$), $BBS_4$, $BBS_5$, MKKS ($BBS_6$), $BBS_7$, TTC8 ($BBS_8$), $BBS_9$, $BBS_{10}$, TRIM 32 ($BBS_{11}$), $BBS_{12}$, $MKS_1$ ($BBS_{13}$), $CEP_{290}$ ($BBS_{14}$), WDPCP ($BBS_{15}$), SDCCAG8 (BBS16), $LZTFL_1$ ($BBS_{17}$) , $BBIP_1$ ($BBS_{18}$)*. However, about 20% of the patients with BBS do not have mutations in these genes. The most common mutations identified in BBS are: *BBS1* – 23.1%, *BBS10* – 20%, *BBS2* – 8.1%, *BBS9* – 6% and *MKKS (BBS6)* – 5.8% [3]. Mutations in *$BBS_1$- $BBS_{18}$* can cause other ciliopathy syndromes [4, 5]. The diagnosis of BBS is mostly established by clinical signs: obesity, rod-cone dystrophy, polydactyly, hypogonadotrophic hypogonadism, mental retardation, hypertension, hyperlipidemia, genitourinary and renal abnormalities. A wide spectrum of clinical signs in patients with BBS is observed, therefore Beales divided the clinical features into the primary and secondary type. Four primary features or three primary features and two secondary features can be used to establish the diagnosis. Primary features include rod-cone dystrophy (90% of patients), truncal obesity, learning disabilities, hypogonadism or genital abnormalities, renal anomalies, polydactyly (68-81%). Secondary features include speech delay, brachydactyly/syndactyly, ataxia, imbalance, developmental delay, eye abnormalities (strabismus, cataracts, astigmatism), hypertonia, diabetes mellitus, cardiovascular anomalies (aortic stenosis, patent ductus arteriosis, cardiomyopathy, atrial/ventricular septal defects), hepatic involvement, craniofacial dysmorphism, Hirschprung disease, anosmia. Rod-cone dystrophy can lead to night blindness, therefore every patient with BBS should start a special educational program very early in childhood. Obesity occurs in most of the cases among patients with BBS. Mean BMI is estimated to be 31.5-36.6 kg/m$^2$. Significant weight gain is observed in the first year of life. Such consequences of obesity as: hypertension, hyperlipidemia, intolerance of glucose are very common. The major cause of morbidity and mortality in patients with BBS are renal malformations, which can lead to end-stage renal disease. Renal malformations include unilateral agenesis, renal dysplasia, calyceal/parenchymal cysts, cortical scarring, vesicoureteral reflux [6]. Each patient with BBS should have regular tests, including: measurements of blood pressure, kidney function tests, ophthalmologic evaluation to determine visual activity, a special diet to avoid obesity, cardiac evaluation, development assessment, neurologic examination, and endocrinology tests including a glucose tolerance test and sex hormone levels [7, 8, 9]. Patients with polydactyly are enrolled for the surgical removal of their accessory digits during the first two years of life.

## CONCLUSIONS

Bardet-Biedl syndrome is a complex, multisystemic developmental disorder associated with ciliary defect. Obesity, polydactyly, retinal degeneration and cystic kidney disease belong to the main cilia-related manifestations. A patient with Bardet-Biedl syndrome needs multi specialist care. Genetic counselling is recommended to estimate the genetic risk of the recurrence of BBS in the family. Each sibling of the affected individual has 25% (1/4) risk of being affected with BBS, and a 50% chance of being an asymptomatic carrier. Parental testing for the mutations, which are identified in the proband are also indicate

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