Hydrometrocolpos and polydactyly: a common neonatal presentation of Bardet-Biedl and McKusick-Kaufman syndromes

Albert David, Pierre Bitoun, Didier Lacombe, Jean-Claude Lambert, Annie Nivelon, Jacqueline Vigneron, Alain Verloes

Abstract

McKusick-Kaufman syndrome (MKKS) is a rare, recessively inherited syndrome reported mainly in young children and is characterised by vaginal atresia with hydrometrocolpos, postaxial polydactyly, and congenital heart defect. Bardet-Biedl syndrome (BBS) is the generic name for a genetically heterogeneous group of autosomal recessive disorders characterised by retinal dystrophy or retinitis pigmentosa (appearing usually between 10 and 20 years of age), postaxial polydactyly, obesity, nephropathy, and mental disturbances, or, occasionally, mental retardation. Typically, MKKS is diagnosed (and reported) in very young children, whereas the diagnosis of BBS often is delayed to the teenage years.

We report here a series of nine patients diagnosed in infancy with MKKS because of the presence of vaginal atresia and postaxial polydactyly, who later developed obesity and retinal dystrophy, thus turning out to be instances of BBS.

The overlap of BBS and MKKS is a real diagnostic pitfall and its importance has to be stressed, for genetic counselling, for clinical management and follow up, and for molecular approaches. The diagnosis of MKKS should be considered with caution in all published cases described exclusively in the neonatal period and in those with mental retardation. We strongly recommend all children seen in neonatal presentation of Bardet-Biedl and McKusick-Kaufman syndromes

Keywords: Bardet-Biedl syndrome; McKusick-Kaufman syndrome; hydrometrocolpos

MKKS was first delineated by McKusick et al in 1964 in two Amish sibships and rapidly confirmed.\(^2\)\(^4\) Over 60 cases have now been reported\(^5\)\(^11\) and autosomal recessive inheritance is clearly established. Cardinal features of MKKS are hydrometrocolpos and polydactyly and it is often reported as the "hydrometrocolpos-polydactyly syndrome". Hydrometrocolpos is present in 80-95% of females and results from either vaginal atresia or imperforate hymen, which leads to the development of an abdominopelvic mass with regional compression and secondary hydron-
associated cases polydactyly is mostly confined to the hands. Chromosome 16 associated cases are least inclined to obesity, whereas chromosome 15 associated cases have early onset, morbid obesity.23–25

We report here a collaborative, retrospective study of nine unrelated BBS girls misdiagnosed as MKKS in the neonatal period, in the presence of genital and digital anomalies.

Case reports

Case 1

Case 1 was born in 1977 to non-consanguineous French parents. At birth, postaxial polydactyly was noted in both feet. At the age of 6 months, the development of an abdominal mass led to the discovery of vaginal atresia complicated by bilateral ureterohydronephrosis. A diagnosis of MKKS was suggested at that time. The patient was lost to follow up until the age of 18, when she was referred for genetic counselling. She presented as a short, obese girl (146 cm, 72 kg). Excessive weight started in infancy. She had RP, a flat ERG, and mild bilateral cataract. She was totally blind on one side and had residual visual acuity of less than 1/10 on the other side, with a 5° tubular visual field. Further investigations showed bilateral kidney atrophy with enlarged calyces. There was no mental retardation. Family history was unremarkable. BBS was finally diagnosed.

Case 2

This girl was born in 1977 to non-consanguineous French parents. At term, birth weight was 3720 g, length was 50.5 cm, and OFC 34 cm. She was noted to have bilateral postaxial polydactyly of both feet and syndactyly IV-V of the left foot. At the age of 4 months, patent urinary tract infection and oedema of the legs led to the discovery of a hydrometrocolpos with vaginal atresia and severe ureterohydronephrosis. A diagnosis of MKKS was made. At the age of 12 years, obesity, developing progressively since the age of 3, and severe myopia were recorded. At the age of 15 years, she was re-evaluated in a genetic centre. She was 154 cm tall and weighed 83.5 kg. She had myopia (~6 dioptres) and RP with low visual acuity (1 to 2/10), tunnel vision of 10°, a flat ERG, and a squint. She was of low normal intelligence. The family history was unremarkable. A diagnosis of BBS was then suggested.

Case 3

An abdominal mass was found in utero in this girl born in 1982 to non-consanguineous French parents. At 38 weeks of gestation, birth weight was 2400 g, length was 44.5 cm, and OFC 32 cm. MKKS was diagnosed in the neonatal period, based on hydrometrocolpos, bilateral ureterohydronephrosis, intercalate polydactyly of the upper limbs, and postaxial polydactyly of the lower limbs. Relative microemilia, hip dislocation, and IUGR were noted. BBS was suggested in infancy because of early obesity, and the ERG, at the age of 1 year, confirmed retinal dysfunction. Mild conductive deafness and scoliosis were noted at ages 4 and 12 years respectively. She menstruated spontaneously at 12 years. At the age of 13½ years, she was 140 cm tall and weighed 60 kg. She had RP with visual acuity <3/10. The family history was unremarkable.

Case 4

This girl was born in 1984 after an uneventful pregnancy to non-consanguineous French parents. She was operated on for hymenal atresia on the second day of life. Postaxial polydactyly was present in the left foot, leading to a diagnosis of MKKS. Impaired renal function was noted at the end of the first week. At the age of 4 months, intestinal occlusion occurred and Hirschsprung disease was found, which required transient ileostomy. Hemeralopia, loss of visual acuity, and progressive reduction of the visual field were noted at the age of 2 years. Visual evoked potentials showed increased latencies and the ERG was flat. A diagnosis of BBS was proposed at that time. Renal insufficiency rapidly worsened and made a renal transplant necessary at the age of 9 years. A rapidly evolving scoliosis was noted in infancy (45° at age 10, 60° at age 12), for which surgical treatment is foreseen. At the age of 12, she was 146 cm tall and weighed 78 kg. She was mildly dysmorphic with a long face, micrognathia, high arched palate, small teeth, short neck, and brachydactyly. She had normal puberty with irregular menses. Basal gonadotrophins and steroid hormones were normal. She was of normal intelligence. The family history was unremarkable.

Case 5

This girl was born in 1985 to first cousin Moroccan parents. Birth weight was 3100 g, length was 44 cm, and OFC 34 cm. Prenatal ultrasonographic investigations showed an abdominal mass, enlarged kidneys, and postaxial polydactyly of all four limbs. These anomalies led the gynaecologist to suggest a diagnosis of MKKS. At birth, vaginal atresia complicated by upper vaginorectal fistula and ureterohydronephrosis seemingly confirmed the diagnosis. A correct diagnosis of BBS was made by the geneticist in the neonatal period, after evaluation of the patient’s brother. In infancy, progressive renal insufficiency appeared, with abnormal corticomedullary differentiation on US scan, but no malformations. Obesity was obvious by the age of 1, and hemeralopia was noted before the age of 3. At the age of 9 years, she had developed atypical RP with pale papillae and gracile retinal vessels. The ERG was flat. Visual acuity was 1/10. At the age of 12, she was 132 cm tall (<3rd centile) and weighed 59 kg. OFC was 52.5 cm. IQ was 56 cm and she required special schooling.

Examination of the older brother of case 5 was prompted by her birth. This boy, aged 5 years at that time, had postaxial polydactyly of all four limbs, obesity (onset at age 3), microgenitalia, and poor vision. Investigations showed atypical RP with abnormal ERG, allowing a firm diagnosis of BBS, and switching the diagnosis of his newborn sister to BBS. At the age of 17, he was 157 cm tall and weighed...
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70 kg. OFC was 55 cm. IQ was 65. Visual acuity was 1/10 bilaterally. The appearance of his kidneys on US was similar to case 5, but without functional consequences. After the birth of case 5, the parents had two further affected girls (born in 1988 and 1995), both with upper limb polydactyly, but no genital anomalies. At the age of 9, the older one was 129 cm tall and weighed 47 kg. OFC was 53 cm. IQ was 77. She showed an asymptomatic renal anomaly similar to her brother and visual impairment, whereas the youngest was already obese (84 cm, 16 kg). Visual impairment has not yet been assessed in the latter.

CASE 6
At birth, this girl, born in 1986 at 38 weeks of gestation to non-consanguineous French parents, was noted to have hydrometrocolpos and an imperforate anus. Birth weight was 3625 g. She developed renal failure in the first few months of life, causing severe failure to thrive. She was started on dialysis by the age of 35 months, and required left sided nephrectomy at the age of 3 and right sided renal transplant at the age of 4. RP was diagnosed at the age of 7 months, with a flat ERG. Profound right sided conductive hearing loss was diagnosed at 18 months. At examination at the age of 6 years 8 months, her height was 111.5 cm (−1 SD), her weight was 19.5 kg (+0.5 SD), and her OFC was 54 cm (+2.5 SD). She was of normal intelligence and had normal visual speech. Visual acuity was <1/10 bilaterally. Her fundi showed a greyish retina without pigment clumps bilaterally.

A diagnosis of BBS was suggested, although the manifestations in this patient had obviously occurred earlier than usually reported, whereas obesity and polydactyly were not present. Although obesity often starts in infancy in BBS, the present case illustrates the fact that early onset of renal insufficiency may delay its development as a consequence of the nephrogenic failure to thrive.

CASE 7
This girl was born in 1989 to non-consanguineous French parents. Postaxial polydactyly of the feet, hydrometrocolpos, bilateral ureterohydronephrosis, urogenital sinus, imperforate hymen, and vaginourethral fistula were noted. Birth weight was 3760 g and length 50 cm. She was diagnosed as having MKKS. At 4 years, obesity and severe myopia (−9/−12 dioptres) were noted, with poor vision. At the age of 5, she was 104 cm tall (−2 SD) and weighed 25 kg (+3 SD). OFC was normal (51 cm). The fundi, at age 7, showed retinal dystrophy with atrophic pigmented epithelium but without pigment clumps, pale papillae, and gracile retinal vessels, compatible with atypical retinitis pigmentosa. She had mild mental retardation. The family history was unremarkable.

CASE 8
This girl was born in 1990 to non-consanguineous Algerian parents. In the prenatal period, an abdominal mass was noted. At birth, the presence of postaxial polydactyly in the right upper limb and in both feet, as well as urogenital sinus and hydrometrocolpos, led to a diagnosis of BBS. Birth weight was 2730 g and OFC 32 cm. Progressive hydronephrosis developed, which was surgically corrected at 4 months. At the age of 6, she was 104 cm tall (−2 SD) and weighed 25 kg (+3 SD). OFC was normal (51 cm). The fundi, at age 7, showed retinal dystrophy with atrophic pigmented epithelium but without pigment clumps, pale papillae, and gracile retinal vessels, compatible with atypical retinitis pigmentosa. She had mild mental retardation. BBS was highly likely. The family history was unremarkable.

CASE 9
An abdominal mass was noted antenatally in case 9. At birth, in 1993, this girl weighed 3280 g, with a length of 48 cm. OFC was 34 cm. Postaxial polydactyly of the left hand and of both feet was noted, as well as vaginal atresia and a huge hydrometrocolpos (300 ml). A diagnosis of MKKS was made. At the age of 3 years, she was 99 cm tall (+2 SD) and weighed 24 kg (+6 SD). She had psychomotor retardation, recurrent UTI despite normal urinary tree imaging, intermittent nystagmus, and abnormal ERG (microvolted potentials), compatible with BBS. A diagnosis of BBS was likely. The family history was unremarkable and the parents were non-consanguineous, but came from the same French village.

Discussion
Hydrometrocolpos is a rare malformation, which may occur in association with other malformations (table 1). Eight of the nine patients reported here showed a convincing BBS phenotype associated with vaginal atresia, and patient 6 was felt to belong to this spectrum because of RP, renal impairment, and vaginal atresia. Although rare, genital anomalies have been reported in BBS for a long time, but their importance in early infancy has never been stressed. The most common problems are vaginal atresia or transverse septum noted in 12 patients reported before our own series (table 2). Rarely, anomalies involving the Müllerian derivatives have been described: Müllerian duct hypoplasia,25 duplication of the uterus,26 and hypoplastic uterus with unilateral ovary.27 Lower urinary tract anomalies include ectopia of the urinary meatus,28 urethral atresia,29 and urogenital sinus.

RP is a hallmark of BBS. In reports of MKKS, RP has been reported twice. In the report of Goecke et al,30 a sibship with consanguineous parents was described, consisting of one girl with postaxial polydactyly and

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<th>With polydactyly</th>
<th>McKusick-Kaufman syndrome</th>
<th>Bardet-Biedl syndrome</th>
<th>Pallister-Hall syndrome</th>
<th>Ellis-Van Creveld syndrome</th>
<th>Orofaciodigital syndrome, type IV</th>
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<td>Without polydactyly</td>
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Table 2  Reported cases of vaginal atresia in BBS

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Note: In Table 2, the cases are listed with their associated diagnoses and additional details such as age at diagnosis or presence of other anomalies. The table highlights the variety of presentations in vaginal atresia cases in BBS, including hydrometrocolpos, vaginal atresia with associated anomalies like haematocolpos, and other urogenital sinus conditions. The references cited include studies where BBS and MKKS have been compared, noting the overlap and confusion in diagnosis, especially in the pediatric and newborn population. The paper discusses the importance of accurate diagnosis and the need for clinical overlap in infancy makes it necessary to establish systematic ophthalmological and neurodevelopmental follow up of all newborns presenting as MKKS. It should be stressed that a part of the overestimation of the mental handicap in BBS probably results from their “slow” behaviour and delayed diagnosis of their poor vision. Renal ultrasonography combined with urography should be performed in all cases of MKKS and detection of impaired concentration ability with the DDAVP test should probably be performed in every case.

For the same reasons, retrospective studies of MKKS should be considered with caution if cases are presented in the neonatal period or are mentally retarded, and all MKKS cases should be re-evaluated for RP and other signs of BBS, as some of these children could be affected by BBS, as illustrated by our experience.

The significant overlap of BBS and MKKS could be of importance for teams dealing with MKKS gene mapping in non-Amish populations. The similarities of MKKS and BBS indicate that the MKKS gene products are likely to act in the same developmental pathway and to interact with the proteins involved in the pathogenesis of BBS.

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