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

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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 infancy with a diagnosis of MKKS to be re-evaluated for RP and other signs of BBS.

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MKKS was first delineated by McKusick *et al*[1] in 1964 in two Amish sibships and rapidly confirmed.[2–4] Over 60 cases have now been reported[5–7] 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 hydronephrosis. Hydrometrocolpos is sometimes associated with urogenital sinus. In males, hypospadias is the only uncommon anomaly. Postaxial polydactyly or, rarely, mesoaxial polydactyly or syndactyly is present in 90% of cases. Congenital heart defects (atrioventricular canal, VSD, hypoplastic left heart) are seen in 10-20% of cases. Mental prognosis is favourable.[7] In two pedigrees derived from the original work of McKusick *et al*[1] in the Old Order Amish, a locus for MKKS syndrome has recently been mapped to 20p12, close to the *jagged1* gene.[8]

BBS is a well known combination[9 10] of hypogenitalism, obesity, postaxial polydactyly, renal dysplasia, retinal degeneration, and mental impairment,[11 12] reported in more than 500 patients.[11–13] Except for visual loss, expression of BBS is highly variable. The diagnosis can only be made if four of the five major manifestations are present in a person or in sibs, and remains a difficult diagnosis in infancy, as the appearance of several key features is delayed. Polydactyly, which is present in 70% of cases, may only affect one limb and is sometimes associated with syndactyly and commonly with brachydactyly. Renal problems are present in 90% of cases,[14] but often remain undiagnosed for years in children with normal renal function if IVP is not performed. Abnormalities include calyceal clubbing, cysts or diverticulae, fetal lobulations, renal cortical loss, and a reduced ability to concentrate urine (sometimes mimicking juvenile nephronophthisis) that may lead to renal failure. Genital anomalies are uncommon, but include vaginal atresia and hypoplasia of the uterus and fallopian tubes. Hirschsprung disease[15–17] and anal atresia are rarely observed. Mental retardation is present in fewer than half of cases. Endocrine anomalies include obesity (90%), diabetes mellitus (50%), hypogonadism in males (88%), and menstrual problems in females (100%).[12] Visual abnormalities characteristically consist of atypical retinitis pigmentosa (RP) with early macular involvement. Electrophysiological studies show a cone-rod dystrophy. Visual impairment is constant but onset is often delayed to the second or the third decade. Most patients are registered blind by the age of 30 years.[12 18]

From a genetic point of view, BBS is a heterogeneous, recessively inherited disease, with at least four loci in 16q13-q22,[19] 11q13,[20] 3p11-p13,[21] and 15q22.[22] There seem to be only weak genotype-phenotype correlations: chromosome 3 associated cases have polydactyly of all four limbs, while in chromosome 15

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 micromelia, 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), micropenis, 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

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 Malian 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 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 and an abnormal ERG. When evaluated at the age of 7 years, she was 128 cm tall and weighed 35.5 kg. ERG showed photopic and scotopic anomalies compatible with a mixed retinal degeneration and the fundi showed RP with a salt and pepper type of pigmentation. Subvalvular aortic stenosis was surgically corrected at the age of 8 years. She required special schooling. At that time, a diagnosis of BBS seemed appropriate. The family history was unremarkable.

Table 1 Syndromes with hydrometrocolpos

With polydactyly	McKusick-Kaufman syndrome
	Bardet-Biedl syndrome
	Pallister-Hall syndrome[42]
	Ellis-Van Creveld syndrome[43–45]
	Orofaciodigital syndrome, type IV[46]
Without polydactyly	Langer-Giedion syndrome[47]

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 pigmentary 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,[26] 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,[12] and urogenital sinus.[29]

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

Table 2 Reported cases of vaginal atresia in BBS

Reference	
26	Vaginal septum and uterus duplex in a 30 year old woman
36, case 3	Vaginal atresia detected at age 13
37	Vaginal atresia + haematocolpos
38	Vaginal atresia, hydrocolpos, and urogenital sinus diagnosed at age 13
30	One girl with hydrometrocolpos and polydactyly, her brother with RP
39	Absence of vagina
28	Vaginal atresia (2 cases)
12	Vaginal atresia
40	Neonatal hydrometrocolpos + meatal ectopia Hydrometrocolpos detected at age 9 + urogenital sinus
34	Persisting urogenital sinus
41	Vaginal atresia + vaginorectal fistula, 1 sister with BBS

hydrometrocolpos who had a brother with atypical RP. The report of Chitayat *et al*[6] (family B) describes a 12 year old girl with postaxial polydactyly, hydrometrocolpos, hydronephrosis, retinal dystrophy, short stature, and normal menarche. Obesity was not mentioned. Recently, Kumar *et al*[31] described a highly inbred Pakistani family in which at least four sibs and two related persons had MKKS. This family showed unusually severe polysyndactyly for MKKS. Males presented with small penis/hypospadias. One of the sibs had Hirschsprung disease (total colonic aganglionosis), bilateral renal cystic dysplasia, and mental delay. From the table in that report, retinal problems are present, although this does not appear in the text of the article. In the light of the present report, we suggest that these three reports deal with BBS instead of the proposed diagnosis, and we have some doubt about the patient reported by Davenport *et al*,[32] who was decribed as MKKS with Hirschsprung disease.

Heart defect has often been considered as a useful clue to the diagnosis of MKKS in the polydactylous male, but is of uncertain use in the differential diagnosis of BBS and MKKS. CHD is rarely mentioned in older publications on BBS, 9/330 in the reviews of McLoughlin *et al*[13 26] and uncommon (9%) in the review by Chitayat *et al*,[6] but it has been noted with high frequency (11/22) in a series of Bedouin BBS patients,[33] where the most frequent diagnoses were bicuspid aortic valve, ASD, pulmonary stenosis, and cardiomyopathy.

Despite the fact that genital anomalies had already been reported in BBS in 1965, the overlap of BBS with MKKS has not received attention until very recently, and the possible confusion between both disorders is still poorly appreciated. The only clear mention of this overlap was in a letter by Schaap *et al*[34] reporting the erroneous diagnosis of MKKS in their previous case report.[35] A reason for this oversight could be that BBS and MKKS have been published in different areas of paediatric and genetic publications, as they are seen (and diagnosed) at different ages by different doctors (neonatologists and paediatric surgeons in infancy, neurologists, endocrinologists, and ophthalmologists later).

Lurie and Wulfsberg[7] in their recent review of MKKS did not discuss BBS at all. They noted that "the frequency of some findings is underestimated [in MKKS]. It is evident, for instance, that not all patients had ophthalmologic examination, and 2 cases of RP may be only 'the tip of the iceberg'". Considering our own experience with MKKS, we cannot accept these statements, but we rather think that MKKS is an overdiagnosed condition, perhaps because of the misleading effect of descriptive names in syndromology: our message is that not all children with hydrometrocolpos and polydactyly have the hydrometrocolpos-polydactyly syndrome.

The consequences of this are straightforward. As long as genetic tests for MKKS or BBS are unavailable routinely, genetic counselling for parents of newborns with hydrometrocolpos and polydactyly should be much more cautious, even when congenital heart defect is present, considering the poor visual prognosis of BBS and the risk of mental impairment. A firm diagnosis of MKKS should be deferred to 5 to 10 years and the possibility of delayed complications should be discussed accordingly. Similarly, this 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.

1 McKusick V, Bauer BL, Koop CE, Scott RB. Hydrometrocolpos as a simply inherited malformation. *JAMA* 1964;**189**:813-16.
2 Dungy CI, Aptekar RG, Cann HM. Hereditary hydrometrocolpos with polydactyly in infancy. *Pediatrics* 1971;**47**:138-41.
3 Kaufman RL, Hartmann HF, McAlister WH. Family studies of congenital heart disease II: a syndrome of hydrometrocolpos, postaxial polydactyly and congenital heart disease. *Birth Defects* 1972;**8**:85-7.
4 Robinow M, Shaw A. The McKusick-Kaufman syndrome: recessively inherited vaginal atresia, hydrometrocolpos, uterovaginal duplications, anorectal anomalies, postaxial polydactyly, and congenital heart disease. *J Pediatr* 1979;**94**:776-8.
5 Cantani A, Tacconi ML, Benincori N, *et al*. Rare syndromes. The Kaufman-McKusick syndrome. A review of the 44 cases reported in the literature. *Ann Genet* 1987;**30**:70-4.
6 Chitayat D, Hahm SY, Marion RW, *et al*. Further delineation of the McKusick-Kaufman hydrometrocolpos-polydactyly syndrome. *Am J Dis Child* 1987;**141**:1133-6.
7 Lurie IW, Wulfsberg EA. The McKusick-Kaufman syndrome: phenotypic variation observed in familial cases as a clue for the evaluation of sporadic cases. *Genet Couns* 1994;**5**:275-81.
8 Stone DL, Agarwala R, Schäffer AA, *et al*. Genetic and physical mapping of the McKusick-Kaufman syndrome. *Hum Mol Genet* 1998;7:475-81.

9 Bardet G. *Sur un syndrome d'obésité infantile avec polydactylie et rétinite pigmentaire (contribution à l'étude des formes cliniques de l'obésité hypophysaire)*. Paris: Thèse 479, 1920.
10 Biedl A. Adiposogenitale dystrophie. *Med Klin* 1922;**18**:1041.
11 Schachat AP, Maumenee IH. The Bardet-Biedl syndrome and related disorders. *Arch Ophthalmol* 1982;**100**:285-8.
12 Green JS, Parfrey PS, Harnett JD, *et al*. The cardinal manifestations of Bardet-Biedl syndrome, a form of Laurence-Moon-Biedl syndrome. *N Engl J Med* 1989;**321**:1002-9.
13 McLoughlin T, Krovetz LJ, Schiebler GL. Heart disease in the Laurence-Moon-Biedl-Bardet syndrome. A review and report of three brothers. *J Pediatr* 1964;**65**:388-99.
14 Harnett JD, Green JS, Cramer BC, *et al*. The spectrum of renal disease in Laurence-Moon-Biedl syndrome. *N Engl J Med* 1988;**319**:615-18.
15 Maeda T, Okazaki K, Tachibana M, *et al*. A case of Hirschsprung's disease associated with Laurence-Moon-Bardet-Biedl syndrome. *Nippon Shokakibyo Gakkai Zasshi* 1984;**81**:912-16.
16 Radetti G, Frick R, Pasquino B, Mengarda G, Savage MO. Hypothalamic-pituitary dysfunction and Hirschsprung's disease in the Bardet-Biedl syndrome. *Helv Paediatr Acta* 1988;**43**:249-52.
17 Islek I, Küçüködük S, Erkan D, *et al*. Bardet-Biedl syndrome: delayed diagnosis in a child with Hirschsprung disease. *Clin Dysmorphol* 1996;**5**:271-3.
18 Fulton AB, Hansen RM, Glynn RJ. Natural course of visual functions in the Bardet-Biedl syndrome. *Arch Ophthalmol* 1993;**111**:1500-6.
19 Kwitek-Black AE, Carmi R, Duyk GM, *et al*. Linkage of Bardet-Biedl syndrome to chromosome 16q and evidence for non-allelic genetic heterogeneity. *Nat Genet* 1993;**5**:392-6.
20 Leppert M, Baird L, Anderson KL, *et al*. Bardet-Biedl syndrome is linked to DNA markers on chromosome 11q and is genetically heterogeneous. *Nat Genet* 1994;**7**:108-12.
21 Sheffield VC, Carmi R, Kwitek-Black A, *et al*. Identification of a Bardet-Biedl syndrome locus on chromosome 3 and evaluation of an efficient approach to homozygosity mapping. *Hum Mol Genet* 1994;**3**:1331-5.
22 Carmi R, Rokhlina T, Kwitek BA, *et al*. Use of a DNA pooling strategy to identify a human obesity syndrome locus on chromosome 15. *Hum Mol Genet* 1995;**4**:9-13.
23 Carmi R, Elbedour K, Stone EM, Sheffield VC. Phenotypic differences among patients with Bardet-Biedl syndrome linked to three different chromosome loci. *Am J Med Genet* 1995;**59**:199-203.
24 Beales PL, Warner AM, Hitman GA, Thakker R, Flinter FA. Bardet-Biedl syndrome: a molecular and phenotypic study of 18 families. *J Med Genet* 1997;**34**:92-8.
25 Bruford EA, Riise R, Teague PW, *et al*. Linkage mapping in 29 Bardet-Biedl syndrome families confirms loci in chromosomal regions 11q13, 15q22.3-q23, and 16q21. *Genomics* 1997;**41**:93-9.
26 McLoughlin TG, Shanklin DR. Pathology of Laurence-Moon-Bardet-Biedl syndrome. *J Pathol Bact* 1967;**93**:65-79.
27 Campo RV, Aaberg TM. Ocular and systemic manifestations of the Bardet-Biedl syndrome. *Am J Ophthalmol* 1982;**94**:750-6.
28 Cramer B, Green J, Harnett J, *et al*. Sonographic and urographic correlation in Bardet-Biedl syndrome (formerly Laurence-Moon-Biedl syndrome). *Urol Radiol* 1988;**10**:176-80.
29 Devarajan P. Obesity and genitourinary anomalies in Bardet-Biedl syndrome after renal transplantation. *Pediatr Nephrol* 1995;**9**:397-8.
30 Goecke T, Dopfer R, Huenges R, *et al*. Hydrometrocolpos, postaxial polydactyly, congenital heart disease, and anomalies of the gastrointestinal and genitourinary tracts: a rare autosomal recessive syndrome. *Eur J Pediatr* 1981;**136**:297-305.
31 Kumar D, Primhak RA. Variable phenotype in Kaufman-McKusick syndrome: report of an inbred Muslim family and review of the literature. *Clin Dysmorphol* 1998;7:163-70.
32 Davenport M, Taitz LS, Dickson JA. The Kaufman-McKusick syndrome: another association. *J Pediatr Surg* 1989;**24**:1192-4.
33 Elbedour K, Zucker N, Zalzstein E, Barki Y, Carmi R. Cardiac abnormalities in the Bardet-Biedl syndrome: echocardiographic studies of 22 patients. *Am J Med Genet* 1994;**52**:164-9.
34 Schaap C, ten Tusscher MP, Schrander JJ, Kuijten RH, Schrander-Stumpel CT. Phenotypic overlap between McKusick-Kaufman and Bardet-Biedl syndromes: are they related? *Eur J Pediatr* 1998;**157**:170-1.
35 Schaap C, de Die-Smulders CE, Kuijten RH, Fryns JP. McKusick-Kaufman syndrome: the diagnostic challenge of abdominal distension in the neonatal period. *Eur J Pediatr* 1992;**151**:583-5.
36 Delthil P, Sourdille J. Les associations pathologiques dans les amblyopies congénitales héréditaires. Intérêt de leur dépistage. *Arch Fr Pediatr* 1965;**22**:177-86.
37 Klein D, Ammann F. The syndrome of Laurence-Moon-Bardet-Biedl and allied diseases in Switzerland. Clinical, genetic and epidemiological studies. *J Neurol Sci* 1969;**9**:479-515.
38 Nadjmi B, Flanagan MJ, Christian JR. Laurence-Moon-Biedl syndrome, associated with multiple genitourinary tract anomalies. *Am J Dis Child* 1969;**117**:352-6.
39 Srinivas V, Winsor GM, Dow D. Urologic manifestations of Laurence-Moon-Biedl syndrome. *Urology* 1983;**21**:581-3.
40 Stoler JM, Herrin JT, Holmes LB. Genital abnormalities in females with Bardet-Biedl syndrome. *Am J Med Genet* 1995;**55**:276-8.
41 Mehrotra N, Taub S, Covert RF. Hydrometrocolpos as a neonatal manifestation of the Bardet-Biedl syndrome. *Am J Med Genet* 1997;**69**:220.
42 Unsinn KM, Neu N, Krejci A, *et al*. Pallister-Hall syndrome and McKusick-Kaufmann syndrome: one entity. *J Med Genet* 1995;**32**:125-8.
43 Akoun R, Bagard M. La maladie d'Ellis-van Creveld. *Algerie Med* 1956;**60**:769-72.
44 Yang SS, Langer LOJ, Cacciarelli A, *et al*. Three conditions in neonatal asphyxiating thoracic dysplasia (Jeune) and short rib-polydactyly syndrome spectrum: a clinicopathologic study. *Am J Med Genet* 1987;**suppl 3**:191-208.
45 Yapar EG, Ekici E, Aydogdu T, Senses E, Gökmen O. Diagnostic problems in a case with mucometrocolpos, polydactyly, congenital heart disease, and skeletal dysplasia. *Am J Med Genet* 1996;**66**:343-6.
46 Meinecke P, Hayek H. Orofaciodigital syndrome type IV (Mohr-Majewski syndrome) with severe expression expanding the known spectrum of anomalies. *J Med Genet* 1990;**27**:200-2.
47 Fryns JP. Trichorhinophalangeal syndrome type 2: another syndromic form of hydrometrocolpos. *Am J Med Genet* 1997;**73**:233.