Acta Medica et Biologica
Vol. 44, No. 3, 157-161, 1996

The Bardet-Biedl Syndrome: A Report of Two Families

Vinchi WANG[1], Man-Tat FONG[2], Tong-Hwey CHANG[3] and Sui-Hing YAN[1]

[1]Departments of Neurology, [2]Nephrology and [3]Ophthalmology, Cardinal Tien Hospital, Hsintien, Taipei, Taiwan

Received November 21 1995; accepted March 12 1996

Summary. **We studied four patients from two families manifesting impaired vision, obesity, hypogenitalism, polydactyly, and mental retardation, features the Bardet-Biedl syndrome, which differs from the Laurence-Moon syndrome by the presence of renal disease and polydactyly. The visual problem is attributed to retinal dystrophy, which was present in all four patients. Renal dysfunction with hypokalemia was noted in only one patient. Close consanguinity occurs between the parents of one family, while there are members with mental disorders but no other manifestations of the Bardet-Biedl syndrome in the other family. As an autosomal recessive disorder, the gene of the Bardet-Biedl syndrome might have an effect on obesity, hypertension, renal disease, and possibly the mental retardation found among the relatives. The relevant literature was reviewed.**

Key words — polydactyly, retinal dystrophy, hypogonadism.

INTRODUCTION

Traditionally, the Laurence-Moon-Biedl syndrome is said to consist of retinal dystrophy, polydactyly, obesity, mental retardation, spastic paraparesis and hypogonadism. The full spectrum is not common.[1] Renal and upper urinary tract abnormalities were recommended to be included in the Laurence-Moon-Biedl syndrome,[2,3] while there was an opposing opinion to separate this syndrome into two disorders:[4] the Laurence-Moon syndrome (LMS) and the Bardet-Biedl syndrome (BBS). LMS outnumbers BBS in spastic paraparesis and ataxia, and the latter exhibits polydactyly more frequently. There are defined criteria for BBS,[5] and the diagnosis should have at least four of the five main features of mental retardation, obesity, polydactyly, retinal degeneration or hypogandism. We report on four members from two families and review the literature.

Correspondence: Vinchi Wang M.D., Department of Neurology, Cardinal Tien Hospital, 362 Chung-Cheng Rd., Hsintein, Taipei Hsien 23137, Taiwan, R. O. C.

CASE REPORT

Our patients came from two families, and their pedigrees are given in Fig. 1. Close consanguinity was observed between the parents of Patient Bl and B2 in Family B. Ancestor tracing revealed no such incidence in Family A. Patient A2 and member A3 are twin brothers. Mental disorder was noted in member A4 and A5, who have no features of BBS. The detailed history of Patient A1 is reported as follows, and the symptoms and signs of the other three patients are listed in the accompanying Table 1.

Patient A1

This 24-year-old male felt weakness of his lower limbs in 1990. Hypokalemia (2.0 mmol/L) was noted on admission to our hospital, in addition to decreased potassium in 24-hour urine collection (13.6 mmol/day). Although lacking proteinuria, there were elevated serum levels with blood urea-nitrogen (BUN) 23 mg/dl, creatinine 1.6 mg/dl and an estimated creatinine clearance of 44.6 ml/min. The hypokalemia was corrected by potassium supplement, and the serum level of creatinine became normal. On examination, the patient was found to have retarded mentality, poor vision, post-axial polydactyly of all four limbs (X-ray films of hands, Fig. 2), hypogenitalism (small testes and penis), and obesity (111 kg, 164 cm in height). Serum levels of cortisol in the morning and in the afternoon were normal (15.0 and 4.6 μg/dl respectively). The sex hormones were checked as follows: testosterone 1.9 ng/ml (3-12), progesterone 0.4 ng/ml (0.1-0.3), FSH 6.6 mIU/ml (<20), LH 5.0 mIU/ml (<25), and

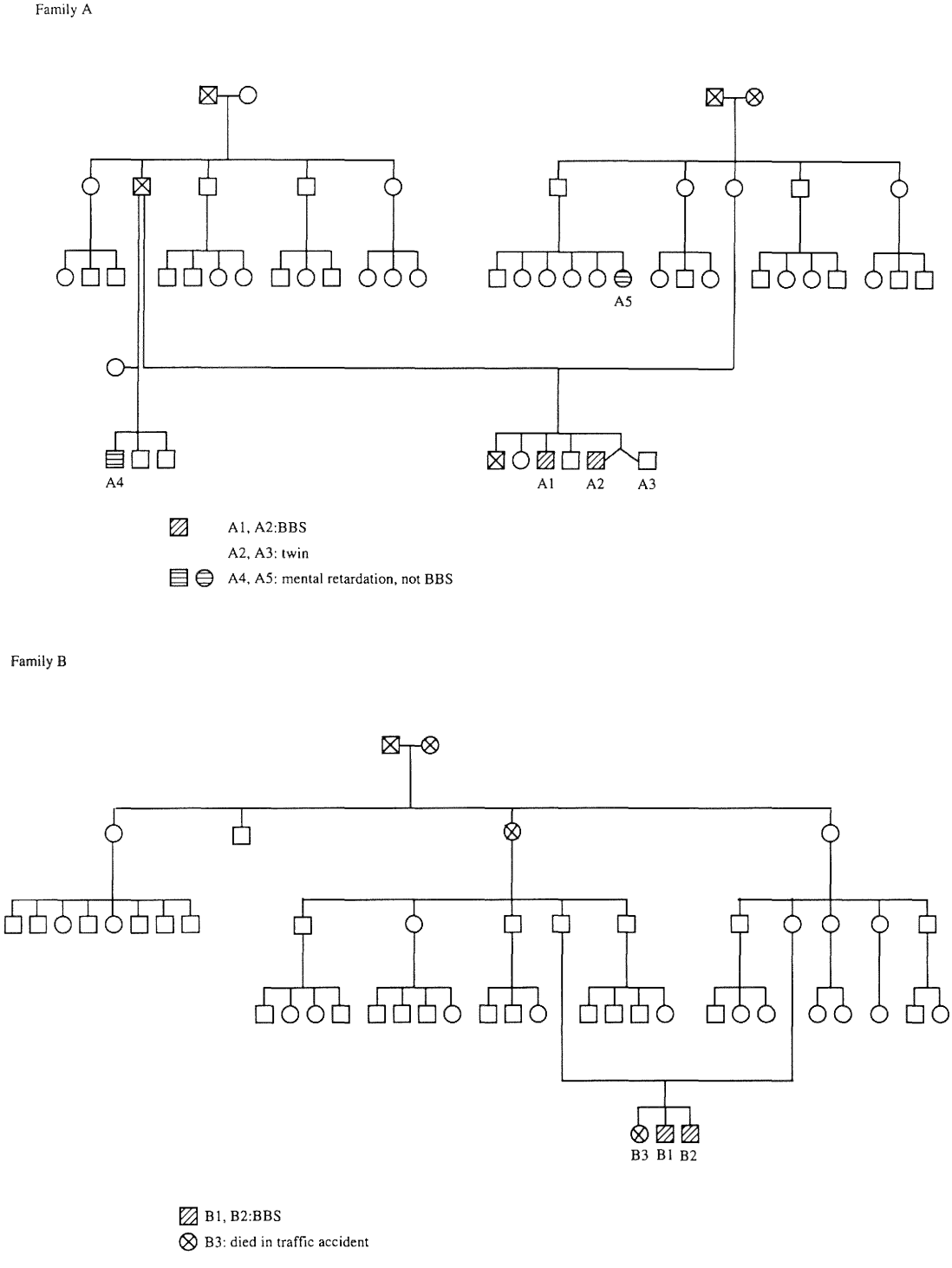

Fig. 1. The pedigrees of our patients in Family A and B. Close consanguity was present in Family B.

prolactin 29.6 ng/ml (2-12). The chromosome study revealed 46 + XY male karyotype. Four years later, he underwent an ophthalmologic examination, which disclosed impaired visual acuity (6/300, ou), refraction error, nystagmus on gazing, color blindness, and diffuse mottling of the retinal pigment epithelium in the fundus. Fluorescence angiography of the fundus showed a diffuse window defect with macula involvement. The IQ check showed a verbal score (VIQ) of 54, performance score (PIQ) of 52, and a full score

Table 1. Clinical manifestations of patients with Bardet-Biedl syndrome in this series

Patient	A1	A2	B1	B2
Age (years)	24	16	16	6
Sex	M	M	M	M
Obesity	++	++	+	+
Retinal dystrophy	+	+	+	+
Visual acuity (with correction)				
od	6/300	6/300	6/200	6/200
os	6/300	6/300	6/150	6/600
Polydactyly				
Hands	+	+	+	−
Feet	+	+	+	+
Syndactylia	−	−	Toe 2,3	Toe 2,3
Hypogonadism	+	+	+	+
Asteatotic skin	+	−	+	+
IQ (V/P/F) score	54/52/49	56/72/63	89/66/76	not tested
Serum creatinine	1.8 mg/dl	0.8 mg/dl	0.7 mg/dl	0.4 mg/dl
Impaired glucose tolerance	+	−	−	−
Cardiac murmur	−	−	−	−

+, present; ++, present and markedly evident; −, absent.

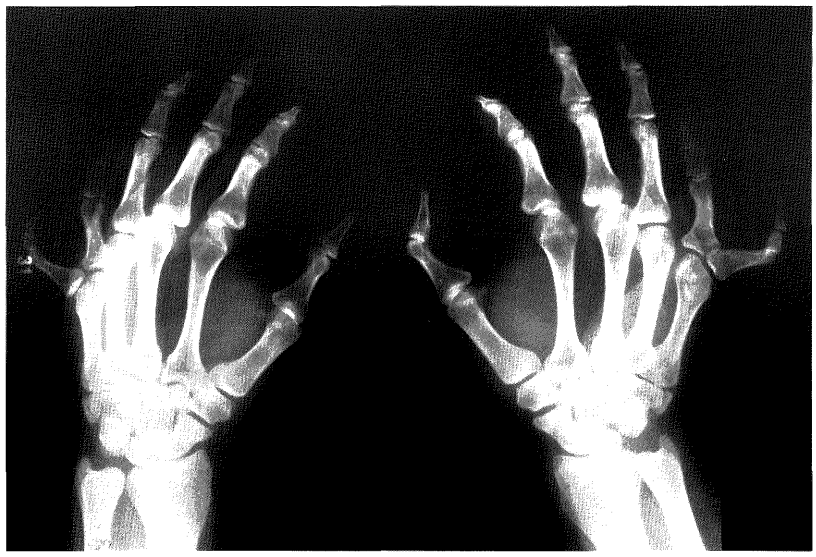

Fig. 2. Roentgenographic films of both hands of Patient A1, showing the polydactyly.

(FIQ) of 49 by the WAIS-R test. The cranial computed tomography (CT) was normal and the neurologic examinations showed no muscle weakness or myotonia, intact sensations, preserved tendon reflexes and a normal gait. Coordination functioned well on finger-to-finger, rapid alternating motions and on tandem gait. The patient is not employed due to his learning disability and inferior poor vision.

DISCUSSION

Our patients fulfilled the diagnostic criteria established by Schachat.[5] Poor vision in these four patients, attributable to tapeoretinal degeneration, was the main problem and the presenting symptom in early childhood. No classic features of retinitis pigmentosa were present on fundoscope examination. Runge et al. suggested that photoreceptor cells were primarily affected, in contrast to the changes in pigment epithelium in mitochondrial cytopathy.[6] There are variable courses of central and peripheral visual functions, and the macula is considered to be susceptible to the degeneration in BBS.[7] With age, the visual acuity and dark-adapted thresholds decline.[8] Other reported ophthalmologic abnormalities include myopia, astigmatism, nystagmus, strabismus and cataracts. Visual field examination could not obtain definite results in our patients, resulting from the nystagmus and poor cooperation related to their mental status. However, we found head turning and tilting on gazing forward in Patient A4, and a visual field defect was suspected. Nystagmus may be related to poor vision since infancy, but gaze-evoked nystagmus of a central origin was present in our patients. Atrophy of cerebellar vermis has been noted on CT and magnetic resonance imaging (MRI) by Rizzo et al.,[9] although the cranial CT of Patient A1 was negative. Electroretinogram studies were not performed for any of the four patients.

The retarded mental ability of our three patients was noted by the WAIS-R IQ test, and the inconsistent verbal-performance difference seemed to be related to vision acuity, which plays an important role in gaining information and education. The CT and the necropsy of brains in the Laurence-Moon-Biedl syndrome are generally normal, but here some atrophy or shrinkage of the frontal lobes was present.[10] On the other hand, there were members (A4 and A5) of paternal relatives in Family A who have mental retardation but no other manifestations of BBS. It is likely that there is a recessive gene present in both of the paternal and meternal relatives, which is related to mental ability. Member A3, the twin brother of Patient A2, has a thin physigue and good school performance. Special education has been recommended for these patients.

An impressive polydactyly is present in all four patients. Interfamilial and intrafamilial variations of BBS are present.[11] Patient B2 has a normal configuration of hands but polydactyly and syndactyly on the toes. Hip dysplasia, skull deformity, genu valgum and tibia vara[12] are other orthopedic problems which are absent in our patients.

The hypogenitalism and obesity might render a diagnosis of Prader-Willi syndrome, in which hypotonia dominates and retinal degeneration is absent.[13] Low serum levels of testosterone and high levels of prolactin were noted in Patient A1. The hypogonadism was suggested to be primary in origin,[14] and Toledo et al. believed an evolving gonadal disorder was present during the early life.[15] In female patients, although there was endocrinal evidence of reproductive dysfunction, hypogonadism was not necessarily present in BBS.[14]

Renal failure is the major cause of death, and renal disease is universally present in BBS.[3] An impaired renal function (elevated serum levels of creatinine and estimated creatinine clearance) was seen in Patient A1 but not in the others. Hypokalemia with proximal muscle weakness may occur, as with Patient A1. The urine pH after ammonium chloride administration was not checked for our patients, but a defect in urine-concentrating ability was reported to be common.[3] Calyceal clubbing and blunting, and calyceal cysts or diverticula by radiology study have been attributed to dysplasia in nature,[3,14] not to a vesicoureteral reflux as suggested by Hurley et al.[15] Due to its overwhelming prognostic importance, renal disease is considered one feature of BBS to differentiate it from LMS.[11]

BBS is an autosomal recessive disorder, common among Arabs in Kuwait.[17] The heterozygotes are predisposed to have obesity, hypertension, diabetes mellitus and renal diseases.[18] Non-allelic heterogeneity and linkage to chromosome 16q[19] has been noted, but Leppert et al. later reported linkage to DNA markers on chromosome 11q.[20] Further genetic studies are warranted for our patients.

REFERENCES

1) Prosperi L, Cordella M, Bernasconi S: Electroretinography and diagnosis of the Laurence-Moon-Bardet-Biedl syndrome in childhood. *J Pediatr Ophthalmol* **14**: 305-308, 1077.
2) Churchill DN, McManamon P, Hurley RM: Renal

disease-a sixth cardinal feature of the Laurence-Moon-Biedl syndrome. *Clin Nephrol* **16:** 151-154, 1981.
3) Harnett JD, Green JS, Cramer BC, Johnson G, Chafe L, McManamon P, Farid NR, Pryse-Phillips W, Parfrey PS: The spectrum of renal disease in Laurence-Moon-Biedl syndrome. *N Engl J Med* **319:** 615-618, 1988.
4) Editorial: Laurence-Moon and Bardet-Biedl syndrome. *Lancet* **2:** 1178, 1988.
5) Schachat AP, Maumenee IH: Bardet-Biedl syndrome and related disorders. *Arch Ophthalmol* **100:** 285-288, 1982.
6) Runge P, Calver D, Marshall J, Taylor D: Histopathology of mitochondrial cytopathy and the Laurence-Moon-Biedl syndrome. *Br J Ophthalmol* **70:** 782-796, 1986.
7) Fulton AB, Hansen RM, Glynn RJ: Natural course of visual functions in the Bardet-Biedl syndrome. *Arch Ophthalmol* **111:** 1500-1506, 1993.
8) Leys MJ, Schreiner LA, Hansen RM, Mayer DL, Fulton AD: Visual acuities and dark-adapted thresholds of children with Bardet-Biedl syndrome. *Am J Ophthalmol* **106:** 561-569, 1988.
9) Rizzo JF, Berson EL, Lessell S: Retinal and neurologic findings in the Laurence-Moon-Bardet-Biedl phenotype. *Ophthalmology* **93:** 1452-1456, 1986.
10) McLoughlin TG, Shanklin DR: Pathology of Laurence-Moon-Bardet-Biedl syndrome. *J Path Bact* **93:** 65-79, 1967.
11) Anadoliiska A, Roussinov D: Clinical aspects of renal involvement in Bardet-Biedl syndrome. *Inter Urol Nephrol* **25:** 509-514, 1993.
12) Motzkin NE, Bianco AJ, Zimmerman D: Tibia vara in a patient with Bardet-Biedl syndrome. *Mayo Clin Proc* **67:** 549-552, 1992.
13) Greer M: Prader-Willi syndrome. In: Rowland LP (ed) Merrit's Textbook of Neurology, 8th edition. Malvern, Pennsylvania. Lea & Febiger, 1989, p 471-472.
14) Green JS, Parfrey PS, Harnett JD, Farid NR, Cramer BC, Johnson G, Heath O, McManamon PJ, O'Leary E, Pryse-Phillips W: The cardinal manifestations of Bardet-Biedl syndrome, a form of Laurence-Moon-Biedl syndrome. *N Engl J Med* **21:** 1002-1009, 1989.
15) Toledo SP, Medeiros-Neto GA, Knobel M, Mattar E: Evaluation of the hypothalamic-pituitary-gonadal function in the Bardet-Biedl syndrome. *Metabolism* **26:** 1277-1291, 1977.
16) Hurley RM, Dery P, Nogrady MB, Drummond KM: The renal lesion of the Laurence-Moon-Biedl syndrome. *J Pediatr* **87:** 206-209, 1975.
17) Teebi AS: Autosomal recessive disorders among Arabs: an overview from Kuwait. *J Med Genet* **31:** 224-233, 1994.
18) Croft JB, Swft M: Obesity, hypertension and renal disease in relatives of Bardet-Biedl syndrome sibs. *Am J Med Genet* **6:** 37-42, 1990.
19) Kwitek-Black AE, Carmi R, Duyk GM, Buetow KH, Elbedour K, Parvari R, Yandava CN, Stone EM, Sheffield VC: Linkage of Bardet-Biedl syndrome to chromosome 16q and evidence for non-allelic genetic heterogeneity. *Nature Genetics* **5:** 392-396, 1993.
20) Leppert M, Baird L, Anderson KL, Otterud B, Lupski JR, Lewis RA: Bardet-Biedl syndrome is linked to DNA markers on chromosome 11q and is genetically heterogeneous. *Nature Genetics* **7:** 108-112, 1994.