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Renal Disease in Bardet-Biedl Syndrome

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Abstract Bardet-Biedl syndrome, a form of Laurence-Moon-Bardet-Biedl syndrome is a rare inheritable disease characterized by the pentad of obesity, mental retardation, pigmentary retinopathy, polydactyly and hypogenitalism. Abnormalities in renal structures and functions are noticed to run a high frequency in this syndrome. Renal failure is recognized to be an important cause of death. We retrospectively reviewed the pattern of renal involvement in our patients and compared it with the past reports. Renal disease was a significant cause of morbidity and mortality in our patients.

Key words Bardet-Biedl syndrome; Renal function

Introduction

Laurence-Moon-Bardet-Biedl syndrome is a rare congenital disorder, inherited in the autosomal recessive mode. The syndrome is characterized by five cardinal features, namely obesity (83% of cases), mental retardation (80%), polydactyly (75%), retinitis pigmentosa (68%) and hypogenitalism (60%).[1] Renal involvement with progressive deterioration in renal function was recognized as a major cause of death.[2,3] Renal disease was so frequently seen that some authors considered it as the sixth cardinal feature.[4,5]

Methodology and Results

Over the past 15 years, six patients were diagnosed to have Laurence-Moon-Biedl syndrome in the Department of Paediatrics, Queen Elizabeth Hospital. We retrospectively reviewed the case records of these patients. Their renal functions were assessed by urine analysis, blood pressure, serum urea and creatinine. Ultrasonography was performed to screen for any structural abnormalities. Follow up investigations would be proceeded if any of the above investigations were abnormal.

Six patients (3 boys and 3 girls) from three Chinese families were identified. Their age ranged from 14-21 years old and the mean duration of follow up was 16 years (range 14-21 years). One patient refused further assessment and was seen once only. Nevertheless, his blood pressure and urinalysis were normal when he was assessed at eleven years of age. All patients showed typical features of Bardet-Biedl syndrome. Their clinical features were summarized in Table 1. Patients 1 & 2, 5 & 6 were siblings from two non-consanguinous families while the parents of patients 3 & 4 were first cousins.

Four patients were found to have renal involvement. Three of them had abnormal renal function. Patient 1 (KMFa) had hypertension with past history of surgical correction for coarctation of aorta. Cardiac catheterization did not show any residual coarctation, which could account for his hypertension. Further investigations showed typical urographic changes and renal biopsy confirmed the presence of underlying kidney disease. His renal function deteriorated despite that his blood pressure was well controlled. Patient 2 (KMFu) had isolated hypertension. Neither her kidney ultrasonography nor serum creatinine showed any significant abnormalities except a small right kidney was detected by serial ultrasound examinations. Her first kidney ultrasound study performed at the age of 12 showed a discrepancy of 1 cm in length in both kidneys. Repeated ultrasound scan 7 years later showed that the difference increased to 1.3 cm suggesting that there might be compensatory hypertrophy in the left kidney. Isotope imaging might be useful to detect any impaired uptakes in the right kidney particularly when the discrepancy in

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Table 1 Summary of clinical features of six patients with Bardet-Biedl syndrome

Patients	Year of birth	Sex	AOP	Presenting complaints	Features of BBS	Outcome
(1) KMFa	1980	M	3 1/2	Heart murmur and polydactyly	Obesity MR Retinitis pigmentosa-Registered blind Polysyndactyly Undescended testes and micropenis Renal COA-repaired	Progressive deterioration in renal function, hypertension
(2) KMFu	1977	F	11	Family screening	Obesity MR Near-blind Poly-brachydactyly	Hypertension, normal renal function on last follow up
(3) LLY	1982	F	1 1/2	Polydactyly, MR	Obesity DM MR Near-blind Polydactyly Progressive renal failure	Died of ESRD at age 14
(4) LKF	1983	M	At birth	Polydactyly Hypospadias Positive family history	Obesity MR Near-blind Polydactyly Hypospadias Undescended testes ASD	ASD repaired, normal renal function
(5) LYT	1983	M	1 1/2	Obesity MR polydactyly	Obesity MR Polysyndactyly Near-blind Micropenis Ectopic testes	Defaulted follow up
(6) LYL	1984	F	At birth	Abdominal mass at birth - urogenital sinus and hydrometrocolpos Positive family history	Obesity MR Near-blind Urogenital abnormalities	ESRD at 11 years old, on regular dialysis

AOP: age of presentation, BBS: Bardet-Biedl syndrome, MR: mental retardation, COA: coarctation of aorta, DM: diabetes mellitus, ESRD: end-stage renal disease, ASD: atrial septal defect.

length continued to progress. However she did not complain of symptoms such as polyuria or polydipsia. Patient 3 (LLY) died from complications of end-stage renal disease. She was first noticed to have abnormal renal function with creatinine clearance of 51 ml/min/1.73m^2 at 10 years old. She was managed conservatively. At age 14, she reached end-stage renal disease with a creatinine clearance of 8 ml/min/1.73m^2. Chronic dialysis was suggested to the parents and the child. After thorough discussion, the family opted for conservative treatment. The child subsequently died from renal failure, pulmonary edema and congestive heart failure. Patient 6 (LYL) reached ESRD at 11 years old. She was maintained initially on peritoneal dialysis and then changed to chronic hemodialysis because of recurrent catheter problems related to previous abdominal surgery. The degree of renal involvement of these 4 patients was summarized in Table 2.

Discussion

Laurence-Moon-Bardet-Biedl syndrome (LMBBS) was first described in literature by two ophthalmologists Zachariah Laurence and Robert Moon in 1866.[6] They reported four siblings with retinitis pigmentosa, lack of

Table 2 Features of renal involvement in four patients

Patients	AOP (renal disease)	Presenting features	Radiological findings	Renal biopsy	HT	Latest renal status
(1) KMFa	16	HT	*USG*: multiple cortical cysts *IVP*: impaired renal function, blunting of calyces, calyceal cysts *DMSA*: decreased uptake in both kidneys	Patches of interstitial chronic inflammatory infiltrate and fibrosis, tubular loss. IF: IgM (1+)	+	HT Cr: 150mmol/L Ur: 7mmol/L
(2) KMFu	12	Urinary tract infections	*USG*: smaller right kidney. Normal echogenicity	ND	+	Normal serum creatinine
(3) LLY	10	Abnormal serum creatinine on routine check	*USG*(age 9,10,13): normal *DMSA*(age 9): normal *DTPA*(age 9): normal	Interstitial fibrosis, tubular atrophy, glomerulosclerosis IF: negative	+	ESRD at age 14 and died of ESRD at 14 years old.
(6) LYL	At birth	Urogenital abnormalities	*IVU*: bilateral hydronephrosis, hydroureters. *VC*: no VUR Urodynamic: normal *USG*: progressive loss of cortical mass	ND	+	ESRD at age 11, on regular dialysis

AOP (renal disease): age of presentation of renal disease; HT: hypertension; USG: ultrasonogram of kidneys; IVP: intravenous pyelogram; DMSA: dimercaptosuccinic acid radionuclide scan; DTPA: diethylenetriamine pentaacetic acid radionuclide scan; VC: voiding cystogram; IF: immunofluorescent study; Cr: serum creatinine; Ur: urea; ESRD: end-stage renal disease; VUR: vesicoureteric reflux; ND: not done.

intelligence, short stature, hypogonadism and spastic paraparesis. There was no further mention of the syndrome until 1920 when George Bardet recognized a group of patients with hypothalamic obesity, hexadacytyly and retinitis pigmentosa. Arthur Biedl, a pathologist and endocrinologist in 1922 also reported 2 siblings with retinitis pigmentosa, polydactyly and mental retardation.[7] Finally in 1925, Solis-Cohen & Weiss considered these conditions to be the same and renamed it as Laurence-Moon-Bardet-Biedl syndrome.[8]

More recently, the condition was recoined on the basis of clinical features as Laurence-Moon (LMS) and Bardet-Biedl (BBS) syndromes.[9] Retinitis pigmentosa, mental retardation, hypogenitalism and spastic paraparesis characterized the former. The latter syndrome, which represented the majority of the published cases, had the main features of retinitis pigmentosa, obesity, postaxial polydactyly, learning disabilities and hypogonadism.[10] In the last 20 years, significant renal involvement was noted in Bardet-Biedl syndrome.[11-13]

In our report, four patients with BBS had renal involvement. Two patients reached end-stage renal disease in early teenage. One patient died because of renal failure and another child underwent renal replacement therapy. One child had typical radiological changes and his renal function deteriorated over time. The last patient had isolated hypertension and a small right kidney. These figures agreed with the past reports of chronic renal failure seen in 30-60% of patients[12, 14] and end-stage renal disease was the most frequent cause of death.[13,15] The degree of renal involvement reported in previous series was summarized in Table 3.

Two of our patients had typical radiological findings (Figures 1, 2 & 3). Radiological features included cysts, blunting and clubbing of calyces, hydronephrosis, hypoplasia, and fetal lobulation of kidneys, which were characteristic features in urography.[16] Despite the frequent findings of calyceal bluntings, vesicoureteric reflux was an unusual feature.[13] The calyceal abnormalities may be dysplastic in nature. Persistent fetal lobulation of kidneys was also noted in these patients and it probably reflected a defect in the maturation of the kidneys.[16] Early sonographic findings of kidneys in BBS were reported recently by Dippell J et al (1998).[17] Serial renal sonography from birth to childhood in his group of seven patients showed characteristic findings including bilateral renal enlargement, increased parenchymal echogenicity and absent corticomedullary differentiation at birth. On follow up scans small cysts at corticomedullary junctions, persisted fetal lobulation and inversion of normal kidney echogenicity became dominant features. Nowadays, the accessibility to ultrasound examination assisted in early

Table 3 Summary of reports on renal manifestation in Bardet-Biedl syndrome

Authors	Year of report	Numbers of patients	Renal manifestations
Hurley et al [11]	1975	9	9 (100%) urographic abnormalities 5 (55%) uremia before 15 years old 2 (22%) died of uremia
Tieder et al [2]	1982	4	3 (75%) decrease renal concentration capacity 3 (75%) renal failure before 12 years old 2 (50%) presented as hypertension 4 (100%) urographic abnormalities
Linne et al [12]	1986	6	2 (33%) uremia 3 (50%) hypertension 3 (50%) recurrent urinary tract infections 3 (50%) urographic abnormalities
William et al [3]	1988	2	2 (100%) uremia at 30 and 37 years old 2 (100%) urographic abnormalities
Harnett et al [13]	1988	20	3 (15%) uremia 50% hypertension 95% urographic abnormalities (1 patient had VUR)
Ucar et al [14]	1997	5	100% urographic abnormalities 20% died from ESRD

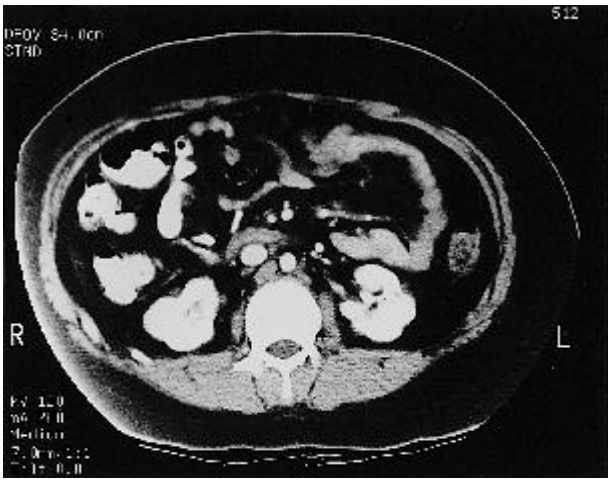

Figure 1 CAT scan of abdomen showed persistent fetal lobulation of kidneys.

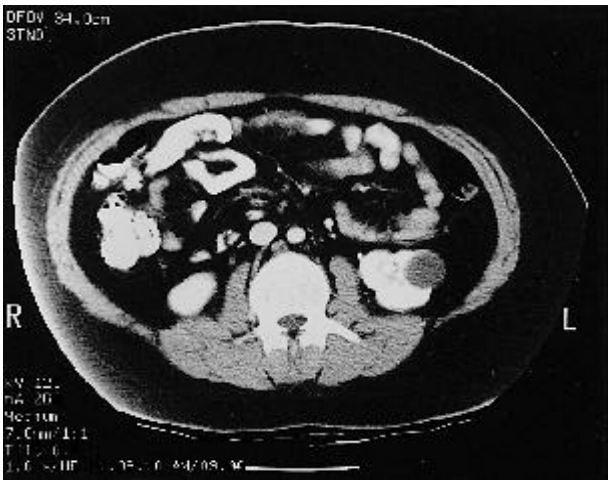

Figure 2 CAT scan of abdomen showed cortical cyst in left kidney.

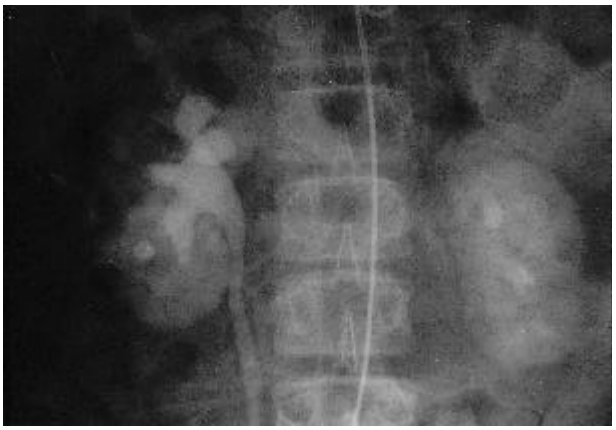

Figure 3 IVU obtained during cardiac catheterization showed blunting of calyces and calyceal cysts over right kidney and delayed contrast excretion in the left kidney.

diagnosis of renal involvement in BBS. The renal ultrasound appearance in neonates with Bardet-Biedl syndrome however, simulated other congenital renal diseases such as autosomal recessive polycystic kidney disease, cystic dysplasia and medullary cystic disease/ nephronophthisis complex.[18] Bardet-Biedl syndrome was considered as one of the differential diagnoses in polydactyly-cystic kidney syndromes.[19]

Hypertension in the absence of renal failure was not an uncommon feature and was reported as high as 50% in one series.[12] In our patients, four out of the six patients were hypertensive and three of them related to underlying renal disease. Harnett et al[13] also reported a significant lower maximal urinary osmolarity in his group of patients when compared with normal subjects. Polyuria and polydipsia were the earliest complaints.[14] Only one patient in our series complained of polyuria and polydipsia but it was due to underlying diabetes mellitus. The defect in urine concentration was believed to result from a decrease in the responsiveness of the kidney to vasopressin.[13,14]

Renal biopsy was performed in two of our patients. Both of them showed significant tubulo-interstitial changes. A wide variety of histological changes had been described in LMBBS.[20] These included interstitial fibrosis, cystic dilatation of tubules, mesangial proliferation and cortical and medullary cysts.[20,21] Price et al[22] reported a marked alteration of the ultrastructure of the glomerular basement membrane (GBM) in his three patients and suggested that these may be the initial renal lesions. These changes included effacement of the trilaminar architecture, segmental and irregular thickening alternating with thinning, rarefaction, accumulation of granular and fibrillary material within the inner third of the GBM. However, it appeared not applicable to every case of BBS.[21] In our patients, electron microscopy did not show the above ultrastructural changes either.

During the period of follow up, one-third of our patients eventually suffered from end-stage renal failure. Mental retardation and visual disability made outpatient peritoneal dialysis particularly continuous ambulatory peritoneal dialysis difficult. Strong family support and the need for a responsible caretaker were mandatory for a good success. Despite these obstacles, successful hemodialysis and renal transplantation had been reported.[23]

Half of our patients in fact had positive family history at presentation. Hence when a new patient was seen, careful family history should be taken. Probands' siblings and relatives should be carefully examined. Despite that the exact gene locus for the pathogenesis of the disease is still unknown, linkage studies have identified several markers in the chromosomal regions 11q13, 15q22.3-q23 and 16q21.[24,25] Nevertheless, the locus responsible for the renal disease is not known. Without an accurate means of prenatal diagnosis, early detection of renal involvement in this group of patients is important.

Conclusion

Renal disease is a common feature in Bardet-Biedl syndrome. Impaired urinary concentration capacity, recurrent urinary tract infections and hypertension are early presentations. Typical radiographic features are seen in many of these patients. Early diagnosis by ultrasonography is possible. On follow up of these patients, regular blood pressure monitoring and serum urea and creatinine level assist in early detection of renal insufficiency.

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Erratum

We regret that Figure 5 was duplicated as Figure 6 in *Body MRI: Its Application in Paediatrics* in October 1999 issue. The correct picture should be follows:

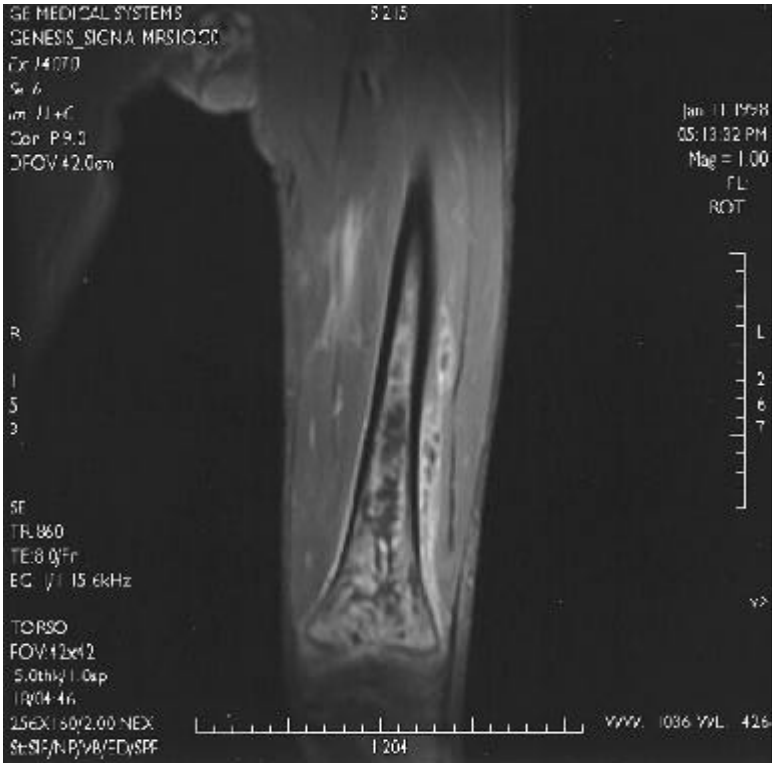

Figure 6 Osteomyelitis. M/15Y. Post-contrast coronal scan showing heterogeneous enhancement at lower end of the femur with adjacent soft tissue involvement.