Bardet-Biedl Syndrome: A Study of the Renal and Cardiovascular Phenotypes in a French Cohort

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Summary

Background and Objectives Bardet-Biedl Syndrome (BBS) is a rare autosomal recessive ciliopathy with a wide spectrum of clinical features including obesity, retinitis pigmentosa, polydactyly, mental retardation, hypogonadism, and renal abnormalities. The molecular genetic profile of BBS is currently being investigated after the recent identification of 14 BBS genes involved in primary cilia-linked disease. This study aims to characterize the renal and cardiovascular presentations and to analyze possible relationships between genotypes and clinical phenotypes.

Design, setting, participants & measurements This clinical study was performed in a national cohort of 33 BBS patients, 22 men and 11 women, all aged >16 years (mean age 26.3 years).

Results Renal abnormalities, including impairment of renal function and signs of chronic interstitial nephropathy of dysplastic nature, were documented in 82% of the patients. Cardiovascular evaluations revealed that this group of young patients had significant cardiovascular risk factors. Hypertension was found in >30% of the patients and hyperlipidemia in >60%, and almost 50% had other metabolic abnormalities. Overt diabetes was present in only 6%. With regard to genotype-phenotype correlation, patients with a mutation in the *BBS6, BBS10*, or *BBS12* gene (10 of 33 patients) had more severe renal disease.

Conclusions Our study results confirm the frequent occurrence of renal involvement in patients with BBS, underscore the high risk of cardiovascular disease in these patients, and provide new information on a possible genotype-phenotype correlation.

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Introduction

Bardet-Biedl Syndrome (BBS, OMIM 209900) is a rare, hereditary, ciliopathy characterized by juvenile obesity, hypogonadism, polydactyly, retinal dystrophy, mental retardation, and renal abnormalities. Hypertension and/or diabetes commonly occur (1,2).

To date, 14 BBS-causing genes have been identified (*BBS1* through *BBS14*; for review see BBS, OMIM 209900). Seven of the most conserved BBS proteins (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, and BBS9) form a stable complex called the BBSome (3), excluding three other proteins, BBS6, BBS10, and BBS12, that are vertebrate-specific chaperonin-like proteins (4). BBS proteins are believed to be involved in the biogenesis and maintenance of the primary cilia/centrosome complex and to be linked with fundamental signaling pathways (5). A BBS gene mutation leads to a disturbance in several signaling routes, in particular, the noncanonical Wnt pathway involved in planar cell polarity that plays a role in the pathogenesis of polycystic kidney disease, which has been described (6,7). Most of the phenotypic traits of BBS have been observed in animal models (8–11). Recent findings in the mouse model of Alström Syndrome (OMIM 203800)—also a ciliopathy closely related to BBS, characterized by renal abnormalities, obesity, and insulin resistance—suggest abnormalities within the centrosome being the cause of this disorder (12).

BBS is of interest to the nephrologist for several reasons. Identification of the genes involved in BBS and related molecular mechanisms can increase our understanding not only of the development of renal pathology in BBS and the overlapping diseases, renal polycystic diseases and ciliopathies, but also of the more common phenotypic traits including obesity, hypertension, and diabetes. Of all features of BBS, the renal defects have been studied most extensively and variability in clinical expression and disease severity have been reported (13,14). In contrast, the cardiovascular profile of BBS patients and cardiovascular risk factors have not yet been well characterized (15,16). Finally, there is still debate over the genotype-phenotype correlation in this pleiotropic disease with possible oligogenic inheritance (17,18).

The objective of this study was to analyze the renal and cardiovascular characteristics of 33 patients affected by BBS and to explore possible correlations between genotype and phenotype.

Materials and Methods

Study Population

The study group consisted of 33 young French adults (aged >16 years) with a mean age (±SD) of 26.3 (7.7) years and a male to female ratio of 2:1. The patients were followed at the center(s) in Strasbourg ($n = 19$), Marseille ($n = 8$), Montpellier ($n = 4$), and Lille ($n = 2$). BBS was diagnosed using the criteria of Beales (1) based on the association of the cardinal symptoms of the syndrome including retinitis pigmentosa, polydactyly, obesity, mental retardation, hypogonadism, and renal abnormalities. The diagnosis of BBS was accepted if three of the aforementioned symptoms were present, or two of the first three symptoms mentioned, or if two symptoms were present and a gene mutation in one of the BBS genes was detected (Table 1). Exclusion criteria included age <16 years, pregnancy, and intercurrent illness.

The data were obtained from patients with BBS followed between March 2003 and March 2007. The study was approved by the Local Ethics Committees and all patients gave informed consent.

Assessments

Renal assessments. Biologic parameters included blood plasma levels of creatinine, potassium, bicarbonates, 24-hour urine analysis of creatinine, protein, and albumin levels. Abnormal urine concentrating ability was defined as the absence of an increase in the osmolality to >750 mOsm/kg H_2O after a 12-hour period of water restriction. Renal ultrasound and abdominopelvic magnetic resonance imaging (MRI) were performed in most patients. GFR was estimated using either direct measurement of urinary clearance creatinine (UCcr) or with the four variable–Modification of Diet in Renal Disease (MDRD) formula (estimated GFR [eGFR]) (19). Staging of chronic kidney disease (CKD) followed the 2005 KDIGO recommendations including markers of kidney damage, proteinuria, hematuria, and abnormalities in imaging tests (20). An abnormal urinary albuminuria was defined by a urinary albumin to creatinine ratio (UACR) >30 mg/g (20).

Cardiovascular abnormalities and risk factors assessments. The personal and familial histories of cardiac symptoms were documented, as well as current cardiovascular treatment. Clinical investigations included fasting blood glucose, total cholesterol, HDL, LDL, fibrinogen, and leptinemia. Glucose intolerance was defined by a plasma blood glucose level of >140 mg/dl but <200 mg/dl in the 2 hours after an oral glucose load and abnormal fasting blood sugar by a fasting plasma glucose (FPG) >110 mg/dl (World Health Organization 1999). Ambulatory BP measurement was performed over a 24-hour period. Electrocardiogram and transthoracic echocardiography were performed to measure the ventricular dimensions in TM mode with an estimation of the left ventricular mass normalized to height$^{2.7}$ as recommended in the obese. Interpretation of these dimensions and calculations of mass were based on the norms agreed upon by the American and European Societies of Echocardiography (21). NCEP-ATP III criteria modified for Europe by the EGIR (22) were used to define an abnormal waist circumference, the ratio of waist to hip circumference, and the diagnosis of metabolic syndrome.

Molecular analyses. The genetic analyses were performed at the Medical Genetics Laboratory, Faculty of Medicine, in Strasbourg (H.D.) and consisted of screening for mutations within the *BBS1* through *BBS12* genes, as described previously (23).

Table 1. Distribution of BBS diagnosis criteria for inclusion

Clinical Symptom	% ($n = 33$)
Retinitis pigmentosa	100
Polydactyly	73
Obesity	70
Mental retardation	55
Hypogonadism	30
Renal abnormalities	21

Statistical Analyses

The results are shown as mean ± SD or percentage specifying the number of patients presenting the sign or symptom of those studied for the variable analyzed. To examine the differences between groups with or without renal diseases, the Fisher exact test was used for categorical data. Statistical significance was accepted for $P < 0.05$.

Results

Renal Phenotypes (Table 2)

Using the MDRD formula, we identified that 36% (12 of 33) of the patients had an eGFR <90 ml/min per 1.73 m^2, of whom 9% (3 of 33) had moderate renal impairment (eGFR between 30 and 60 ml/min per 1.73 m^2). Direct measurement of UCcr in 31 patients revealed that 48% (15 of 31) of them had a UCcr below 90 ml/min and 19% (6 of 31) had moderate renal impairment (UCcr <60 ml/min).

Abnormalities suggesting tubulointerstitial lesions were frequent with abnormalities in urine concentration in 63% of patients. Proteinuria was found in 33% and the UACR was abnormal (>30 mg/g) in 31% of patients. Of the nine patients with elevated UACR, four were hypertensive and one was both hypertensive and diabetic. Microscopic hematuria was found in only two patients.

Renal ultrasound was performed in all patients and MRI was performed in 24 of 33 patients. Nine patients could not undergo MRI because of obesity. Abnormal renal development was confirmed in almost 50% of the patients (Table 2). Renal asymmetry or atrophy and undifferentiated aspect of one or both kidneys were noted in 12% of the patients. The mean size of the kidneys (±SD) in the group was however normal at 115 (12) × 47 (9) mm. Cysts were generally cortical, and in four patients they were solitary. The imaging

Table 2. Characteristics of renal functional abnormalities

Renal Symptoms	% (Patients with Signs/Tested)
Renal function	64 (21/33)
eGFR ≥90 ml/min per 1.73 m^2	
eGFR ≥60 and <90 ml/min per 1.73 m^2	27 (9/33)
eGFR <60 ml/min per 1.73 m^2	9 (3/33)
Proteinuria (>0.15 g per 24 hours)	33 (10/30)
UACR (>30 mg/g)	31 (9/29)
Hematuria (>10 red cells per mm^3)	6 (2/33)
Impaired urinary concentrating ability	63 (19/30)
Morphological abnormalities	
renal cysts	23 (6/23)
caliceal malformation	50 (13/26)
fetal lobulation	33 (8/24)
CKD stage	
CKD stage 1	33 (10/33)
CKD stage 2	27 (9/33)
CKD stage 3	9 (3/33)

eGFR by the MDRD formula; UACR >30 mg/g. CKD stage 1 = normal renal function (eGFR ≥90 ml/min per 1.73 m^2) and markers of kidney damage (proteinuria, hematuria, or morphological abnormalities); CKD stage 2 = eGFR <90 ml/min per 1.73 m^2 and markers of kidney damage; CKD stage 3 = eGFR <60 ml/min per 1.73 m^2.

methods did not reveal the presence of corticomedullary cystic dysplasia or more severe forms of dysplasia, such as horseshoe kidney or agenesis. Finally, 36% of the patients presented with signs suggesting CKD stage 2 (27%) to CKD stage 3 (9%) and overall renal abnormalities, including at least renal function impairment and/or signs of tubulointerstitial lesions of dysplastic nature and/or impaired urinary concentration ability, were documented in 82%.

Cardiovascular Phenotypes (Table 3)

There was a strong prevalence of systemic hypertension (36%) in this young population. Three patients had a past history of antihypertensive treatment and ambulatory BP measurement showed mean values >130/80 mmHg over a period of 24 hours in seven patients. Of the ten hypertensive patients, eight were obese and four showed signs of CKD. All evaluated patients had a normal electrocardiogram.

In those who underwent transthoracic echocardiography, no valvulopathy or structural abnormalities were noted. Two patients had a known history of ventricular communication. Left ventricular dilation was demonstrated in only one patient and left ventricular hypertrophy (LVH) was found in 5 of 29 of patients. Of these five patients, three were hypertensive. A slightly abnormal ejection fraction (54%) was found in only two patients.

Table 3. Cardiac phenotype characteristics

	% (Patients with Signs/Tested)
Systemic hypertension[a]	36 (10/28, 4 with CKD)
Abnormal electrocardiogram	0 (0/33)
Abnormal echocardiography	
left ventricular dilatation[b]	4 (1/29)
left ventricular hypertrophy[c]	17 (5/29)
abnormal ejection fraction (<55%)	6 (2/29)
valvulopathy or other cardiac abnormalities	0 (0/29)

[a]Mean arterial blood pressure 24 hours >130/80 mmHg.
[b]Abnormal left ventricular diastolic diameter if >5.9 cm in men and >5.3 cm in women.
[c]Abnormal left ventricular mass if >48 g/$m^{2.7}$ in men and >44 g/$m^{2.7}$ in women.

Cardiovascular Risk Factors (Table 4)

In addition to the high prevalence of hypertension, dyslipidemia was found in 53% of patients with an increase in the LDL cholesterol >160 mg/dl in 9% of the patients and a decrease in HDL cholesterol <40 mg/dl in 47% of the patients. Details on smoking history were not available. None of the patients had a past history or a family history of cardiovascular disease.

Eleven of 33 patients (33%) presented with an abnormal glucose metabolism. Two were treated for type 2 diabetes mellitus whereas FPG and 2-hour plasma glucose (2-h PG) excluded diabetes in others. Glucose intolerance was demonstrated in six patients and three other patients had an abnormal FPG. Hypertriglyceridemia (>150 mg/dl) was found in 22% of patients. A possible endothelial dysfunction was suggested by the presence of hyperfibrigenemia (>4 g/L) in 27% of patients and of microalbuminuria in 31% of patients. Obesity, which is a cardinal sign in this syndrome, was present in 70% of patients (body mass index, >30 kg/m^2). This obesity was mainly android in distribution as the abdominal adiposity, as measured by waist circumference, was elevated in 79% (22 of 28) of obese patients. The ratio of waist to hip circumference was abnormal in 50% of patients (14 of 28). An associated hyperleptinemia (blood leptinemia >11 μg/L) was noted in 90% of patients. The aforementioned abnormalities allow the conclusion that a metabolic syndrome existed in 45% of patients (13 of 29) to be reached (22).

Genotype-Phenotype Correlations

A *BBS1* gene mutation was found in 37% of patients (12 of 33), a BBS10 mutation in 15% (5 of 33), and a

Table 4. Cardiovascular risk factors distribution

	% (Patients with Signs/Tested)
Classic cardiovascular risk factors	
PMH or family history of cardiac disease	0 (0/33)
arterial blood pressure raised	36 (10/28)
diabetes mellitus	6 (2/33)
dyslipidemia	53 (17/32)
LDL ≥160 mg/dl	9 (3/32)
and/or, HDL ≤40 mg/dl	47 (15/32)
Other cardiovascular risk factors	
metabolic abnormalities	
glucose intolerance	25 (6/24)
abnormal fasting glucose	9 (3/33)
triglycerides >150 mg/dl	22 (7/32)
obesity (BMI >30 kg/m^2)	70 (23/33)
central obesity[a]	79 (22/28)
metabolic syndrome	45 (13/29)
left ventricular hypertrophy	17 (5/29)
micro- or macroalbuminuria	31 (9/29)
stage 3 CKD[b]	9 (3/33)
hyperfibrinogenemia (>4 g/L)	27 (9/33)
hyperleptinemia (>11 μg/L)	90 (27/33)

PMH, past medical history; BMI, body mass index.
[a]Central obesity if waist circumference is >94 cm in men or >80 cm in women.
[b]CKD stage 3 = GFR <60 ml/min per 1.73 m^2.

BBS12 mutation in 12% (4 of 33) (Table 5). In 9% of patients (3 of 33), the gene mutation has not yet been defined but is believed to relate to a hitherto unknown gene. In this cohort, no mutation was found in the BBS3, BBS7, or BBS8 gene. There was only one case of triallelism (*BBS12* homozygous mutation, *BBS3* heterozygous mutation).

The small numbers in each genotype group do not allow firm conclusions regarding particular genotype-phenotype correlations. Interestingly, among the patients presenting with the BBS1 mutation, only 6% (2 of 12) were obese and had CKD. However, all patients with the BBS12 mutation (4 of 4) had CKD and most were obese (3 of 4) and had metabolic abnormalities (3 of 4). A similar tendency appeared to be present in patients with a BBS10 mutation; 4 of 5 patients were obese and 1 of 5 had a metabolic syndrome. Thus, considering the three most common genes, it appeared that the BBS1 phenotype was more attenuated than the BBS10 and BBS12 phenotypes.

Another pertinent way to explore genotype-phenotype correlations is to investigate phenotypic differences between patients presenting with mutations on the BBSome, that is, the well-conserved *BBS1*, *BBS2*, *BBS4*, *BBS5*, *BBS7*, *BBS8*, and *BBS9* genes, and patients with BBS mutations in other BBS genes (*BBS6*, *BBS10*, and *BBS12*) found only in vertebrates (Table 6). It appeared that there are no obvious significant differences in the cardiovascular risk phenotype between the two categories of genes. Conversely, patients with mutations of specific vertebrate genes *BBS6*, *BBS10*, and *BBS12* presented with a far worse renal phenotype because 70% (7 of 10) had a diagnosis of CKD compared with 15% (3 of 20) of patients with BBSome genes mutations ($P < 0.005$).

Discussion

This study aimed to describe renal phenotypes in a population of 33 young adults (mean age 26.3 years) with BBS and is the first to characterize cardiovascular phenotypes and to evaluate cardiovascular risk factors in these patients. Our study is also one of a few studies that have investigated possible relationships between genotype and phenotype in BBS patients.

One of the important findings of our study is the frequency of occurrence of renal disease, whatever its nature, of 82%, which confirms that kidney involvement is one of the cardinal signs of the syndrome. Moreover, almost one third of our cohort of young adults presented with signs compatible with CKD stages 2 and 3. It is of interest to note that in a group of older patients, O'Dea *et al.* pointed out that 100% of their patients with BBS had renal structural abnormalities and 25% had impaired GFR by the age of 48 years (24). In the same way, Webb *et al.* recently reported a Newfoundland series of BBS with a prevalence of CKD stage 3 (eGFR <60 ml/min per 1.73 m^2) reaching 47% (20 of 43) at a median age onset of CKD of 58

Table 5. Distribution of BBS genotypes of the 33 patients included in this case series

Patient	Sex	Age	Mutations	Type of Mutation
1	**M**	**34**	***BBS1: M390R/M390R***	**MS**
2	**M**	**21**	***BBS1: M390R/M390R***	**MS**
3	**M**	**18**	***BBS1: M390R/M390R***	**MS**
4	**M**	**35**	***BBS1: M390R/M390R***	**MS**
5	**M**	**38**	***BBS1: M390R/M390R***	**MS**
6	**F**	**53**	***BBS1: M390R/M390R***	**MS**
7	**M**	**17**	***BBS1: M390R/M390R***	**MS**
8	**F**	**28**	***BBS1: M390R/E384X***	**HC**
9	**F**	**21**	***BBS1: M390R/E549X***	**HC**
10	**M**	**21**	***BBS1: M390R/E549X***	**HC**
11	**F**	**39**	***BBS1: R429X/N***	**Truncated**
12	**M**	**28**	***BBS1: R429X/N***	**Truncated**
13	**M**	**27**	***BBS2: P134fsX200/L209fsX229***	**Truncated**
14	**M**	**19**	***BBS4: Q247X/Q247X***	**Truncated**
15	**F**	**31**	***BBS5: K41fsX52/K41fsX52***	**Truncated**
16	**F**	**27**	***BBS5: K41fsX52/K41fsX52***	**Truncated**
17	**M**	**21**	***BBS5: K41fsX52/K41fsX52***	**Truncated**
18	**F**	**21**	***BBS5: K41fsX52/K41fsX52***	**Truncated**
19	M	24	*BBS6: (429delCT433delAG) D143fsX158/S479X*	Truncated
20	**M**	**22**	***BBS9: del exons 8 + 9 hmz***	**Truncated**
21	**M**	**20**	***BBS9: R278X/R278X***	**Truncated**
22	F	21	*BBS10: C91fsX95/C91fsX95*	Truncated
23	F	28	*BBS10: C91fsX95/L348fsX360*	Truncated
24	M	30	*BBS10: C91fsX95/Y321X*	Truncated
25	M	34	*BBS10: R49W/R49W*	MS
26	M	21	*BBS10: R49W/L414S*	MS
27	M	23	*BBS12: F372fsX373/F372fsX373*	Truncated
28	M	37	*BBS12: P159L/I346T*	MS
29	M	23	*BBS12: R355X/R355X*	Truncated
30	F	19	*BBS12: T257fsX266/T257fsX266*	Truncated
31	M	19	No known mutation	
32	F	26	No known mutation	
33	M	21	No known mutation	

Type of mutation: MS, missense mutation; HC, heterozygous composite. In bold, BBS gene owning to the BBSome; BBS6, BBS10, and BBS12 encode for the chaperonin-like proteins (see text).

years (25). Stage 4 CKD (eGFR <30 ml/min per 1.73 m^2) concerned 20% of patients and 14% progressed to ESRD. Theses studies confirmed the high prevalence of CKD in BBS patients after the fourth decade and strengthen our observation that renal symptoms may be present and detected early in young patients who will develop renal impairment with a slow progression to ESRD.

The observed frequencies of caliectasis and of persistent fetal lobulation in our series are suggestive of abnormal renal maturation being a prominent pathologic feature. Historically, these abnormalities were even more frequently detected by using intravenous urography, which is more sensitive for assessment of classic features such as calyceal diverticuli and communicating calyceal cysts. Actually, reported frequencies of cystic abnormalities in BBS patients greatly vary, from 10% to 72% (14,24). These differences can also be attributed to the clinical heterogeneity in both the disease presentation and natural occurrence of cysts. In BBS, cysts distribution is reminiscent of nephronophthisies rather than polycystic kidney disease with microcysts arising at the corticomedullary junction, or ectasias of the collecting ducts which are not easily detectable by imaging modalities (14,24).

The renal dysfunction in BBS points toward a tubulointerstitial process with a proteinuria rarely exceeding 1 g per 24 hours and abnormalities in urine concentration, suggesting a dysfunction in the collecting duct system. The few pathologic studies published in the literature agree with these findings. However, glomerular lesions characterized by thickening of the basement membrane seen on electron microscopy have also been reported (26,27). The ex-

Table 6. Renal and cardiovascular genotype-phenotype relationship; BBSome genes compared with other genes

Signs/Symptoms	Mutations in BBS1 through BBS11 Gene (Excluding BBS6 and BBS10) (n = 20/33)	Mutations in BBS6, BBS10, or BBS12 Gene (n = 10/33)	Unknown (n = 3/33)
CKD (stages 2 and 3) (n = 12/33)	15% (3/20)	70% (7/10)	66% (2/3)
Proteinuria (n = 10/30)	25% (5/20)	20% (2/10)	100% (3/3)
Abnormal urine concentration (n = 19/30)	55% (11/20)	70% (7/10)	33% (1/3)
Renal cysts (n = 6/26)	20% (4/20)	20% (2/10)	0% (0/3)
Caliectasis (n = 13/26)	35% (7/20)	50% (5/10)	33% (1/3)
Hypertension (n = 10/28)	25% (5/20)	20% (2/10)	100% (3/3)
Diabetes (n = 2/33)	10% (2/20)	0% (0/10)	0% (0/3)
Dyslipidemia (n = 17/32)	45% (9/20)	50% (5/10)	100% (3/3)
Obesity (n = 23/33)	60% (12/20)	80% (8/10)	100% (3/3)
Metabolic syndrome (n = 13/29)	35% (7/20)	40% (4/10)	66% (2/3)
LVH (n = 5/29)	5% (1/20)	10% (1/10)	100% (3/3)

CKD stage 2: eGFR <90 ml/min per 1.73 m^2 and markers of kidney damage (proteinuria, hematuria, or morphological abnormalities). CKD stage 3: eGFR <60 ml/min per 1.73 m^2.

istence of an abnormal ACR in 31% of patients suggests associated glomerular disease, which could also be the consequences of long-term hypertension or diabetes. In this context, proteinuria could also be considered as an additional marker of the high global cardiovascular risk in these patients.

Patients with predominant tubulointerstitial lesions generally have a slower rate of progression to ESRD. Nevertheless, in BBS patients, this classic slow rate could be accelerated by the concomitant occurrence of hypertension or diabetes and the longitudinal follow-up of our cohort could provide, in the future, interesting data on the specific rate of progression in BBS patients with early diagnosis of CKD.

Limited published data on the cardiovascular risk of BBS patients are available (16). Despite their young age, nearly half of our young patients already presented criteria putting them in a high-risk group for developing cardiovascular events. In our series the classic cardiovascular risk factors appear to be overrepresented compared with those in the French general population (28). Dyslipidemia associated with low HDL cholesterol was found in nearly half of the patients and a third of the patients already showed signs of hypertension of which the prevalence should also increase with age. The prevalence of diabetes or glucose intolerance is comparable with published data (between 6% and 48%) and is probably also prone to increase with age.

This study, evaluating the often ignored cardiovascular aspect of this syndrome, is one of the largest published studies. Congenital cardiomyopathy or LVH have been suggested to be of limited value in establishing the diagnosis of BBS. Elbedour *et al.* performed systematic echocardiography in 22 patients with BBS and found seven patients (32%) with cardiac abnormalities (three with congenital malformations and two with LVH) (15). In our series, only two patients (6%) had a past history of ventricular communication and LVH was found in 17%, most of whom were hypertensive, suggesting that LVH could result from end-organ damage. This relatively low frequency of LVH is intriguing given the expected additive effect of obesity on cardiac function.

The exploration of possible correlations between genotypes and phenotypes in the cohort of BBS patients is hampered by the genetic heterogeneity of the disease. Moore *et al.* could not find any correlation between the genotype and the frequency of occurrence of phenotypic traits such as blindness, obesity, hypertension, or diabetes (18). They hypothesized that because of this absence of a correlation, all the BBS genes are involved in an identical cellular process. This hypothesis is reinforced by several observations: (*1*) the colocalization of various BBS proteins at the level of the primary cilia and the centrosome; (*2*) the recent description of a core-complex of BBS proteins, the BBSome (3); (*3*) the similarity of phenotypes observed in BBS mouse models, whatever gene is removed (5). Nevertheless, in our series, the phenotypic differences we observed seem to occur according to the mutations involving either the genes owning to the BBSome or the other genes of the vertebrate-specific chaperonin-like proteins group (BBS6, BBS10, and BBS12). The patients with mutations in the latter genes seem to have a more severe renal phenotype compared with the patients with mutations in the BBSome. This hypothesis is corrob-

orated by a recent study in which removal of these genes in the zebrafish lead to a more severe phenotype in a synergistic manner (4). The presented results illustrate the importance of further studies to better understand BBS at the molecular level as well as its genetic epidemiology.

Obviously, this study has some limitations. As previously mentioned, we conducted a cross-sectional study in a population of young patients with BBS. All the patients were at an early stage of the disease and a longitudinal survey is needed to confirm the prognostic importance of their high cardiovascular and renal risk factors. *BBS1* through *BBS12* genes have been exhaustively screened for mutations but *BBS13* and *BBS14* are currently being investigated.

In conclusion, this study highlights the high prevalence of renal disease in BBS and reaffirms the need for early diagnosis and treatment. Cardiovascular risk factors need to be considered and, if present, treated early to prevent subsequent complications. Extensive future genotyping studies may reveal genotype-phenotype correlations, allowing early diagnosis and better understanding of the pathophysiology of associated cardiovascular abnormalities. Longitudinal study of the patients presented herein will provide valuable data on the morbidity, mortality, and natural progression of cardiac and renal disease involvement. Although BBS is a rare disorder, it is of great interest to the nephrologist as genetic and molecular mapping will contribute to the general understanding of inherited kidney ciliopathies, and of cardiovascular problems in chronic renal failure. Thus, the role of the nephrologist is pivotal in the management of this multisystem syndrome affecting both the cardiovascular and the renal systems.

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Disclosures

None.

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