THE RENAL LESIONS IN BARDET BIEDL SYNDROME: HISTORY BEFORE AND AFTER THE DISCOVERY OF BBS GENES

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INTRODUCTION

The BBS is a genetic disorder characterized by retinal degeneration, polydactyly, obesity, learning disabilities, hypogenitalism and renal anomalies. Various renal lesions of the Bardet-Biedl syndrome (BBS) have been described including 1. fetal lobulation, 2. calyceal clunbbing, 3. focal sclerosing glomerulonephritis, 4. interstitial nephritis, 5. changes in the glomerular basement membrane. Polyuria, polydipsia and chronic renal failure have been also reported in many case reports [Regenbogen and Eliahou, 1993].

NO KIDNEYS AT THE BEGINNINGS

The familiar origin of the syndrome begins in the half of 18th century, with Maupertuis and Réaumur describing hereditary polydactyly.
While polydactily was widely known since ancient times [see essay on Wikiwand], the hereditary aspect of the malformation starts in late 1700.
Pierre-Louis Moreau de Maupertuis, (born Sept. 28, 1698, Saint-Malo, France—died July 27, 1759, Basel, Switz.), was known, as a mathematician and astronomer, to popularize Newtonian mechanics [Encyclopaedia Britannica].
In *Système de la nature ou Essai sur les corps organisés* (1751) he studied the transmission of polydactyly in four generations of a Berlin family, giving the first report of the hereditary of this trat [Cobb 2006].
Renè-Antoine Ferchault de Réaumur (1683-1757), the famous French scientist who gave his name to the temperature scale, is reported by [Huxley, 1860] to have analyzed data from three families (named Kelleia) from Malta with hereditary polydactily.

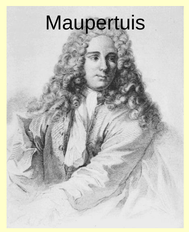
Similarly to polydactyly, also progressive blindness was largely known since ancient times; however, the possibility of a hereditary form of blindness was first noted in the early 19th century by Martin. He reported, in the Baltimore Medical and Physical Recorder (1809), of a Maryland family of Franch origin (Lecomptes family) whose members suffered progressive blindness noticed a familial case of blindness [Harper 2008].
While none of these authors were actually describing cases of BBS, they are reported here because they first force the observation of subsequent researchers towards hereditary forms of polydactily and blindness.

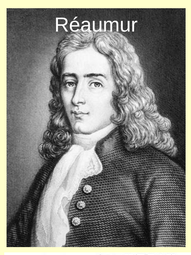
Indeed, soon after, [von Graefe Albrecht, 1858] and thereafter Liebreich first reported a familiarity in the combination of blindness and deafness. Also this report was not BBS, but Retinitis pigmentosa, but, again, sets the stage for finding of combined forms of hereditary traits, and these observations are, in fact, cited by Laurence and Moon in their work (see below).

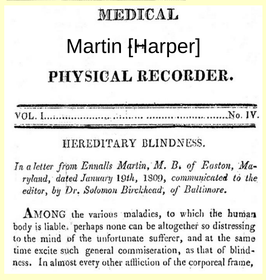
Another essential discovery that must be acknowledged for the definition of BBS was the invention of the ophtalmoscope in 1851 by Hermann von Helmholtz (1821-1894), which allowed fundus observation and thus the defition of retinitis pigmentos.

John Zachariah Laurence (1829-1870), a surgeon and ophtalmologist at the ophtalmologic hospital Southwark, promoted the use of the ophtalmoscope in England. Together with his collegue at the same hospital, Robert C Moon, house surgeon, in 1866, they were the first to describe, using the ophtalmoscope, a familial case of combined retinal degeneration, obesity, and cognitive impairment.

In the first years of the new millennium, the medical attention was shifted to the hypotalamic forms of obesity-hypogonadism thanks to the work of a neurologist, Joseph Babinski (1857-1932), a pharmachologist, Alfred Fröhlich (1871-1953) [1901] and a neurosurgeon, Harvey Cushing (1869-1939) [1912]. Again, in the history of science, we see how important advances in a specific field come from a completely different field, and how this unpredictable contamination was a necessary step for the first definition of our disease.






MEDICAL
Martin [Harper]
PHYSICAL RECORDER.

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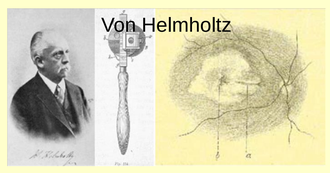
HEREDITARY BLINDNESS.

In a letter from Ennalls Martin, M. D. of Easton, Maryland, dated January 19th, 1809, communicated to the editor, by Dr. Solomon Birckhead, of Baltimore.

AMONG the various maladies, to which the human body is liable, perhaps none can be altogether so distressing to the mind of the unfortunate sufferer, and at the same time excite such general commiseration, as that of blindness. In almost every other affliction of the corporeal frame,



The strong influence of Fröhlich is visible when the first report of a BBS case was singularly attributed to a pituitary malfunction.

Around this period a certain number of obesrvations of obesity, polydactyly and retinitis pigmentosa are reported by several authors: In 1887 Darier reports association of retinitis pigmentosa and polydactyly [1887]. In 1989 De Cyon [1989] presents the case of 12-year old boy with obesity, growth and mental retardation, familiarity for polydactyly. In 1898 Ed Forunier reports retinitis pigmentosa and syndactyly [1898]. In 1913 Rozabel Farnes [1913] reports adiposo-genital syndrome with polydactyly. In 1914 an Italian radiologist, Mario Bertolotti presented the case of Marguerite Catt, 39 years old, with polydactyly, mental retardation, obesity, retinitis pigmentosa, hypogonadism [1914] In 1918 J Madigan and THomas Verner Moore [1918] a case of mental retardation, obesity, hypogonadism, retinitis pigmentos, tapering toes.

Finally, in 1920 a French medical student, **George Bardet** (1885-1966), in his medical degree thesis, collects all these cases and his own observation of a familial case of obesity, hexadactyly, retinitis pigmentosa and hypogenitalism and proposes the existence of a triad [1920]. He discusses this finding under the view of the current paradigm of hypophyseal/hypothalamic obesity:

"Two congenital malformations (hexadactyly and retinitis pigmentosa) in a child who became obese from birth. What is the gland which can be incriminated? An epiphyseal or superrenal origin can be eliminated immediately. One can think of the possibility of thyroid insufficiency but our little sick child presented no symptoms of myxedema […].We believe this case must be attached to a very special clinical variety of hypophysis obesity".

Bardet's triad (obesity, polydactyly, retinitis pigmentosa) gained success after the father of modern endocrinology, **Arthur Bield** (1869-1933), in 1922 observed further cases of the syndrome. Biedl named the syndrome adiposo-genital dystrophy, and taught it was of cerebral origin, in line with the paradigms of that period.
The disease was hence named Laurence-Moon-Bardet-Biedl Syndrome, although later Laurence-Moon and Bardet-Biedl syndromes were then considered different entities or part of the same disease spectrum.
As first conclusion, we should note that, in the first half of 1900, the BBS was definitely defined, but **none of these authors noticed modifications in the kidney function**, which is today acknowledged as an important signature of the syndrome.
It is even intriguing that, even in 1995, in an excellent editorial of the syndrome by George Bray on Obesity Research, the kidney manifestations are completely ignored by the author [Bray 1995].

Arthur Biedl

KIDNEY FAILURE WAS FINALLY RECOGNIZED

Awareness of the renal involvement in BBS starts in the late 60's: McLoughlin and Shanklin [1967], Nadjmi [1969], Hurley [1975] and Falkner [1977].
Nadjmi et al [1969] first reviewed necropsies of BBS and found a high incidence of uremia: they suggest that a high incidence of associated renal anomalies with renal failure is a major cause of early death in BBS patients.

The diffusion of the technique of precutaneous kidney biopsy by Nils Alwall (1904-1986) allowed Hurley et al [1975] to first report histological data from a series of nine BBS children. The results were quite variable, from mesangial proliferation to sclerosis, cystic dilatation of the tubules, cortical and medullary cysts, periglomerular and interstitial fibrosis, chronic inflammation.

Falkner et al [1977] found in a 24-mth old child with BBS right sided vescico-ureteral reflux, cystocele, UTI, growth arrest of the right kidney. They also confirm the mesangial hypercellularity by percutaneous biopsy.
In the 1990 the incidence of renal abnormalities in BBS was finally determined to be very high: up to 90% of the patients, and therefore become a new signature of the syndrome, more than 50 years from its initial definition [Regenbogen 1993]. In the meanwhile the spectrum of renal abnormalities was stably defined as [Regenbogen 1993]:
Functional: polyuria, polydipsia, aminoaciduria, reduction of maximum concentrating capacity, chronic renal failure, hypertension
Macroscopic: fetal lobulation, cystic dysplasia and calyceal cysts, small kidneys, calyceal clubbing or blunting
Microscopic: swelling of endotelial cells, tubular and interstitial nephritis with glomerulosclerosis.

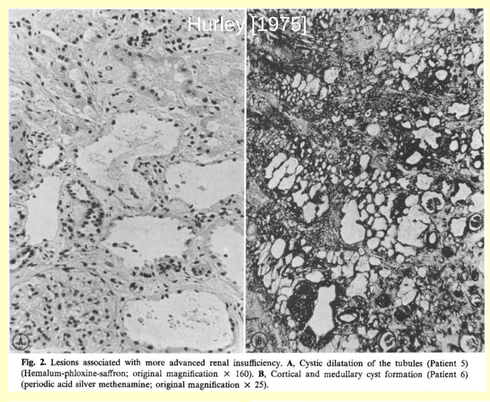


Fig. 2. Lesions associated with more advanced renal insufficiency. A, Cystic dilatation of the tubules (Patient 5) (Hemalum-phloxine-saffron; original magnification × 160). B, Cortical and medullary cyst formation (Patient 6) (periodic acid silver methenamine; original magnification × 25).

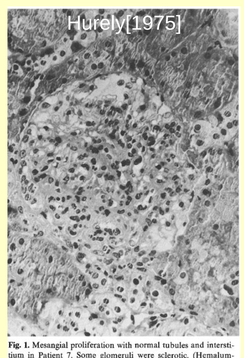


Fig. 1. Mesangial proliferation with normal tubules and interstitium in Patient 7. Some glomeruli were sclerotic. (Hemalum-phloxine-saffron; original magnification × 400.)

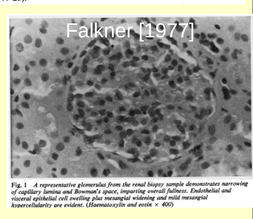


Fig. 1. A representative glomerulus from the renal biopsy sample demonstrates narrowing of capillary lumina and Bowman's space, imparting overall fullness. Endothelial and visceral epithelial cell swelling plus mesangial widening and mild mesangial hypercellularity are evident. (Hematoxylin and eosin × 400)

THE RENAL LESIONS AFTER BBS GENES

The quest for the genes occurred in two phases: from 1993 to 2000 a genetic mapping was pursued, with the identification of several DNA loci involved in the disease. In 2000 the identification of the first BBS gene (now they number 21), MKKS, based on the similarity between the BBS and the McKusick-Kaufman syndrome (MKS) occurred. In 2003 Ansley et al demonstrated that mammalian BBS8 gene was restricted to ciliated cells. This finding raised the hypothesis that BBS proteins play a role in cilia function.

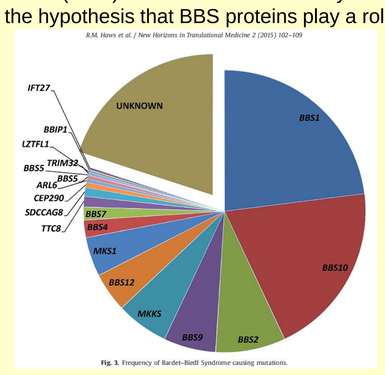


Fig. 3. Frequency of Bardet–Biedl Syndrome causing mutations.

The genes that, when damaged, give rise to BBS

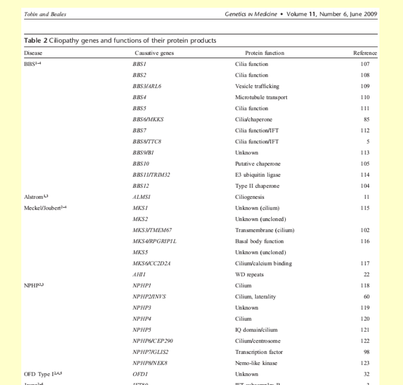

Tobin and Beales — Genetics in Medicine • Volume 11, Number 6, June 2009

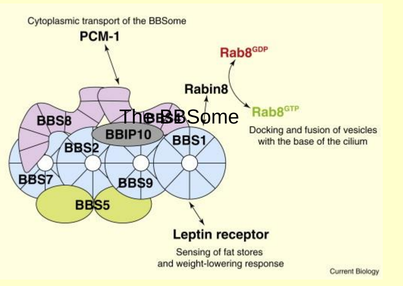
Table 2 Ciliopathy genes and functions of their protein products

Disease	Causative genes	Protein function	Reference
BBS[1–4]	*BBS1*	Cilia function	107
	BBS2	Cilia function	108
	BBS4/ARL6	Vesicle trafficking	109
	BBS4	Microtubule transport	110
	BBS5	Cilia function	111
	BBS6/MKKS	Cilia/chaperone	85
	BBS7	Cilia function/IFT	112
	BBS8/TTC8	Cilia function/IFT	5
	BBS9/B1	Unknown	113
	BBS10	Putative chaperone	105
	BBS11/TRIM32	E3 ubiquitin ligase	114
	BBS12	Type II chaperone	104
Alstrom[5,6]	*ALMS1*	Ciliogenesis	11
Meckel/Joubert[7–9]	*MKS1*	Unknown (cilium)	115
	MKS2	Unknown (unclomed)	
	MKS3/TMEM67	Transmembrane (cilium)	102
	MKS4/RPGRIP1L	Basal body function	116
	MKS5	Unknown (unclomed)	
	MKS6/CC2D2A	Cilium/calcium binding	117
	AHI1	WD repeats	22
NPHP[9,1]	*NPHP1*	Cilium	118
	NPHP2/INVS	Cilium, laterality	60
	NPHP3	Unknown	119
	NPHP4	Cilium	120
	NPHP5	IQ domain/cilium	121
	NPHP6/CEP290	Cilium/centrosome	122
	NPHP7/GLIS2	Transcription factor	98
	NPHP8/NEK8	Nemo-like kinase	123
OFD Type I[5,6]	*OFD1*	Unknown	32
Jeune[5,6]	*IFT80*	IFT subcomplex B	3
Ellis van Creveld[5,6,3]	*EVC1*	Cilium	124
	EVC2	Unknown	125

Putative role of BBS genes

After the period of discovery of BBS genes and the construction of concept of the BBSome, some new insights in the renal pathology of BBS have been addressed. First, the gene-phenotype relationship has been studied in much detail, with a categorization of mutations leading to various associations of the visual, metabolic and kidney phenotypes.
Second, a number of transgenic mice are now available for testing of pathogenetic hypotheses and new pharmachological approaches.
Risk factors for the development of the renal disease have been studied in a very large cohort (350 BBS cases), and the usefulness of renal transplantation has been demonstrated in a separate study.

A contribution for low protein diet in the preservation of renal function in BBS has also been reported. Finally, a study from one of us (MZ, 2016) showed combined impaired water handling in BBS, possibly mediated by the tubulopathy.



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