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Report

Cutaneous findings in Bardet-Biedl syndrome

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Abstract

Background Bardet-Biedl syndrome (BBS) is a rare, pleiotropic syndrome and member of a diverse group of disorders known as ciliopathies. Improved understanding of dermatoses in BBS will further understanding of the syndrome and will help define the role of dermatologists in providing care for patients with BBS. The purpose of this study was to describe the cutaneous phenotype of BBS in patients attending a large, multispecialty BBS clinic.

Methods All patients attending the multispecialty BBS Clinic at the Marshfield Medical Center over a 12-month period were invited to participate. Complete cutaneous examinations were performed by a board-certified dermatologist, and comprehensive physical examinations were performed by clinic physicians. Molecular genetic results were obtained when available. Comprehensive laboratory studies were performed in each patient including fasting blood sugar and thyroid and renal function.

Results Thirty-one individuals ranging in age between 2 and 69 years (median age, 12 years) participated in the study. Cutaneous findings were present in all subjects. Keratosis pilaris was present in 80.6% of subjects, and seborrheic dermatitis was present in 19.3%. Obesity, a cardinal feature of BBS, was present in the majority of subjects (90.3%) and was accompanied by known obesity-related dermatologic disorders.

Conclusions Cutaneous disorders are common in BBS and suggest disturbance of keratinization and keratinocyte function as well as systemic consequences of BBS on skin health. Increased prevalence of skin barrier dysfunction in this ciliopathy demonstrates the importance of dermatologist contribution to health care in BBS.

Introduction

Ciliopathies are a diverse group of diseases resulting from dysfunction in hair-like organelles (cilia) extending from the cell surface. The primary cilia, present in almost all mammalian cells including dermal and epidermal cells, are critical to cellular communication, signal transduction, and control of cell growth while motile cilia line the epithelia in the brain, respiratory tract, inner ear, and fallopian tubes and power sperm movement. Defects in motile cilia result in laterality anomalies in thoracoabdominal organs, infertility, and chronic respiratory disease.[1–3] Ciliopathies are divided into primary (nonmotile) ciliopathies, such as polycystic kidney disease and Bardet-Biedl syndrome, and motile ciliopathies, represented by diseases such as Kartagener's syndrome and primary ciliary dyskinesia.[4,5] Cutaneous lesions have been reported in these and other ciliopathies; however, prospective, observational studies of skin diseases in ciliopathies are lacking in the literature.[6–9] The pleiotropic ciliopathy Bardet-Biedl syndrome (BBS; MIM 209900) provides a mechanistic model for disorders of the cilia and offers the opportunity to explore cutaneous diseases among ciliopathies.[10]

BBS is a rare genetic disease with a prevalence in the nonconsanguineous populations of Northern Europe and North America ranging between 1 in 100,000 (North America) and 1 in 160,000 (Switzerland).[11] Common features of BBS include truncal obesity usually associated with hyperphagia, postaxial polydactyly, renal and urinary tract anomalies, early-onset severe retinal degeneration, cognitive disabilities, and gonadal abnormalities. Twenty-three causative genes have been identified in BBS, accounting for 80% of affected individuals.[12] The protein products of each of these genes are critical to primary cilia homeostasis, growth, and function. A distinct association of BBS with cutaneous diseases has been suggested, although not definitively identified.[8,9,13,14] It has been established that primary cilia are prevalent in epidermal and dermal cells and perform vital functions for integument health beginning in embryogenesis and persisting thereafter, suggesting that cutaneous disorders would be anticipated in BBS and other ciliopathies.[1,2,15–17] Furthermore, BBS is associated with comorbidities that impact skin health such as obesity, diabetes mellitus, dyslipidemia, chronic kidney and liver disease, and endocrine dysfunction.

We aim to describe the cutaneous phenotype of BBS in children, adolescents, and adults attending a large, multispecialty BBS clinic. Systemic features of BBS in the subjects are discussed to provide context for the cutaneous features. We conclude that the high prevalence of skin barrier dysfunction in this ciliopathy demonstrates the importance of dermatologist contribution to health care in BBS.

Materials and methods

The study cohort comprised individuals meeting diagnostic criteria for BBS[13] and currently receiving care at the BBS Center of Excellence at Marshfield Medical Center. Participants were enrolled during a 12-month period (March 2017–February 2018). Informed consent/assent was obtained from each participant and/or parent/legal guardian. Complete cutaneous examinations were performed by a board-certified dermatologist (T.M., C.G.). Molecular genetic testing results were collected when available. Comprehensive laboratory studies were performed in each participant including fasting blood sugar, hemoglobin A1c, thyroid function, renal function, and hepatic function. Body mass index (BMI) was calculated in kilograms per meter squared. BMI percentiles for children were determined using Centers for Disease Control published growth charts.[18] Chronic kidney disease (CKD) stage was determined based on estimated glomerular filtration rate calculated using the Schwartz-Lyon formula for individuals ≤18 years and the Chronic Kidney Disease Epidemiology Collaboration equation.[19,20] Dyslipidemia in all subjects was determined based on National Cholesterol Education Program guidelines.[21] The study protocol was approved by the Marshfield Clinic Health System Investigational Review Board.

Results

Twenty-four children and seven adults (17 males/14 females) were enrolled in the study. The patients provided a broad age spectrum with pediatric patients ranging in age from 2 to 18 years and adult patients ranging in age from 23 to 69 years. Dermatologic examination and comprehensive evaluation were performed in all patients. Eight distinct BBS genotypes were represented (BBS1, BBS2, BBS4, BBS5, BBS6, BBS7, BBS10, and BBS12) in the cohort. Four individuals had no prior genetic testing. A single participant underwent genetic testing without identifying a causative mutation. Systemic health conditions including obesity, hypothyroidism, diabetes type 1 & 2, and CKD were identified based on review of subjects' medical records (Table 1).

Varied cutaneous lesions were identified in the subjects (Table 2). Dermatoses were identified in all patients, and multiple forms of cutaneous findings were present in 25 individuals. Sixteen individuals had four or more cutaneous findings. Keratosis pilaris (KP) and xerosis were the most common dermatologic findings, identified in 80% of patients. KP was usually identified in common locations and often associated with xerosis; however, extensive distribution of KP was observed in four subjects. Seborrheic dermatitis was present in six (19%) subjects and located in typical locations such as eyebrows, scalp, and nasolabial folds.

Multiple, widespread pigmented nevi have been described previously in BBS.[13,14] In our cohort, nevi were present in 54.8% of subjects. Junctional nevi were most commonly observed (48.4%). A congenital nevus was observed in only one subject, compound nevi in two subjects, and dermal nevi in three individuals. Widespread distribution of nevi was present in

Table 1 Patient clinical characteristics

Characteristics	Children	Adults	All
n	24	7	31
M/F	15/9	3/4	18/13
Age (median and range [years])	9.5 (2–18)	43 (23–69)	12 (2–69)
BMI	*n* (%)	*n* (%)	*n* (%)
Lean	1 (4.2)	1 (14.2)	2 (6.5)
Overweight	1 (4.2)	0 (0)	1 (3.2)
Obese	22 (91.7)	6 (83.3)	28 (90.3)
Dyslipidemia	2 (8.3)	2 (28.3)	4 (12.9)
Chronic kidney disease	0 (0)	4 (47.1)	4 (12.9)
Diabetes			
T1DM	1 (4.2)	0 (0)	1 (3.2)
T2DM	0 (0)	3 (42.8)	3 (42.8)
Hypothyroidism	1 (4.2)	1 (14.2)	2 (6.5)

BMI, body mass index; chronic kidney disease stage 3 or higher; F, female; M, male; T1DM, diabetes mellitus type 1; T2DM, diabetes mellitus type 2.

Table 2 Dermatoses

Dermatoses	*n* (%)	Dermatoses	*n* (%)
Common		Less common	
Keratosis pilaris	25 (80.6)	Alopecia	2 (6.5)
Nevi	17 (54.8)	Cherry angiomas	2 (6.5)
Acanthosis nigricans	11 (35.4)	Onychodystrophy	2 (6.5)
Striae	10 (32.2)	Ichthyosis vulgaris	1 (3.2)
Pigmentation abnormalities[a]	9 (29.0)	Psoriasis	1 (3.2)
Acne vulgaris	7 (22.5)	CARP[b]	1 (3.2)
Seborrhiec dermatitis	6 (19.3)	Intertrigo	1 (3.2)
Acrochordons	4 (12.9)	Lichen simplex	1 (3.2)
Eczema	4 (12.9)	Asteatotic dermatitis	1 (3.2)
Hidradenitis suppurativa	3 (9.6)	Hyperhidrosis chronicus	1 (3.2)

[a]Pigmentation abnormalities include traumatic hyperpigmentation, café au lait spots, confetti macular hypopigmentation, and solar lentigines.
[b]CARP, Confluent and reticulated papillomatosis.

three subjects. Diverse pigmentation abnormalities were observed in 29% of subjects including café-au-lait spots in two of the subjects, confetti macular hypopigmentation in one subject, and solar lentiginoses in one subject. Postinflammatory hyperpigmentation associated with self-injurious behaviors (e.g., picking, scratching) was identified in three subjects.

Dermatoses that were present but uncommon in the BBS cohort included hidradenitis suppurativa present in 9.6% of subjects while psoriasis, ichthyosis vulgaris, and confluent and reticulated papillomatosis (CARP) were identified in three separate subjects (Table 2). Hypertrophic scarring was evident in one subject. Frontal alopecia was present in one male pediatric subject. Hypertrichosis and hirsutism were not identified in any subject.

Systemic diseases associated with dermatoses including obesity, CKD, dyslipidemia, and hypothyroidism were frequently present in subjects (Table 1). Obesity was particularly common in both children and adults (90.3%), consistent with previously published results.[13,22] Skin findings associated with obesity including acanthosis nigricans (35.4%), striae (32.2%), and acrochordons (12.9%) were identified. Acanthosis nigricans was present in the only subject with diabetes mellitus type 1 and two subjects with diabetes mellitus type 2 as well as in nearly 30% of individuals without diabetes. All subjects were screened for thyroid dysfunction, and normalization of thyroid function was achieved for a minimum of 6 months prior to evaluation. A female renal transplant recipient receiving tacrolimus therapy was noted to have alopecia, a known complication of tacrolimus therapy.[23] CKD and dyslipidemia were primarily observed in adults.

Cutaneous features were identified in all individuals with BBS, and the individual genotype did not predict dermatoses in our cohort (Table 3).

Discussion

This report is the first prospective, observational study examining cutaneous disorders in BBS, a model ciliopathy for understanding the pleiotropic manifestations of ciliary dysfunction. Detailed dermatologic examination was combined with systemic health, genetic, and laboratory investigation in children, adolescents, and adults with BBS. Systemic conditions including obesity, diabetes mellitus, hypothyroidism, and CKD were identified. Eight distinct BBS genotypes were represented in the observational study. The study does not clearly differentiate the impact of systemic conditions, such as obesity and diabetes, or genotype on skin health from the underlying ciliopathy. However, the diversity and extent of skin disease suggests a potential role for primary cilia dysfunction to contribute to cutaneous disease in BBS.

KP, a disorder of keratinization of the follicular infundibulum, was the dominant feature in our patients and was observed in both children and adults. KP has been reported as an associated cutaneous feature of obesity,[24–26] although the prevalence of KP in our cohort of BBS patients appears to be much higher (80.6%) compared to the prevalence in other obese populations.[24,25] Our study design does not allow us to determine if the KP observed in patients with BBS is a result of obesity or a reflection of primary cilia dysfunction in keratinocyte differentiation and maturation.[15,16,26] The stratum corneum is devoid of cilia; however, keratinocytes and other dermal cells are subject to cellular signaling mechanisms mediated by primary cilia.[1,15,16,27] Given the high prevalence of KP in our BBS cohort, a defect in epidermal maturation and keratinization appears to be a potential feature of BBS.

Obesity and associated metabolic complications including hyperinsulinism, dyslipidemia, and diabetes mellitus are widespread in BBS as well as in the overlapping ciliopathy of Alstöm syndrome.[28] The predominant cutaneous findings in our cohort are described in obese populations. Considering the prevalence of obesity in the cohort, it is not surprising that striae, acanthosis nigricans, acrochordons, and intertrigo were observed to be similar to published reports in the general obese population.[24–26,29] Obesity is a comorbidity factor in psoriasis, and individuals with BBS have been previously reported to have psoriasis.[8,9] Obesity, likewise, is a comorbidity for hidradenitis suppurativa and CARP and may contribute to the appearance of these skin disorders in our cohort.[30,31]

Table 3 Frequency of dermatoses in Bardet-Biedl syndrome (BBS) genotypes

Gene (*n*)	Keratosis pilaris *n* (%)	Nevi *n* (%)	Acanthosis nigricans *n* (%)	Striae *n* (%)	Pigmentation abnormalities *n* (%)	Acne vulgaris *n* (%)	Seborrhiec dermatitis *n* (%)
BBS1 (5)	3 (60)	4 (80)	3 (60)	1 (20)	2 (40)	2 (40)	1 (20)
BBS2 (4)	3 (75)	4 (100)	1 (25)	1 (25)	1 (25)	0 (0)	1 (25)
BBS4 (2)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BBS5 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
BBS6 (2)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BBS7 (1)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BBS10 (7)	6 (86)	5 (71)	3 (43)	5 (71)	2 (29)	3 (43)	2 (29)
BBS12 (4)	3 (75)	0 (0)	1 (25)	1 (25)	1 (25)	1 (25)	0 (0)
Unknown (5)	5 (100)	3 (60)	3 (60)	2 (40)	3 (60)	1 (20)	1 (20)

In contrast, nevi, hyperpigmentation, hypopigmentation, or hypopigmented lesions were not observed more commonly in our cohort than expected. A previously published case report of multiple nevi in a patient with BBS suggested that nevi may be a secondary feature of BBS.[14] This study does not confirm the increased presence of nevi in the syndrome. Pigmentation abnormalities were also not unusually common in our patients. The role of primary cilia in regulation of melanogenesis and pigmentation in human skin has been previously examined *in vivo*.[32] Melanogenesis was reported to be inversely related to primary cilia function; however, our findings do not support the presence of impaired melanogenesis.

The integument is essential to human health, and mounting evidence demonstrates a vital role for primary cilia in the epidermis, dermis, and skin appendages including the hair follicle and sebaceous gland.[1,2,15,16] The primary cilia are first identified during embryogenesis mediating cell–cell signaling between epidermal cells and the underlying dermal mesenchyme.[15,16,33] Primary cilia, present in most cell types in the skin, engage signaling pathways including Hedgehog, Notch, Wingless, and receptor tyrosine kinases to mediate integument development and homeostasis.[34–36] Epidermal cilia have a vital impact on skin homeostasis, keratinocyte differentiation, wound repair, and response to epidermal stress.[1] Dermal primary cilia exert an essential role in hair follicle and sebaceous gland morphogenesis as well as during hair follicle cycling in postnatal life.[1,2]

Improved knowledge of integumentary health in BBS and other ciliopathies may provide previously unappreciated insight into the role of the primary cilia in skin health and disease. Furthermore, therapeutic interventions for obesity, a significant morbidity in BBS and other ciliopathies, employ melanocortin-4 receptor (MC4R) agonist therapy.[37,38] Hyperpigmentation and other skin changes induced by melanocortin receptor activation are expected with MC4R therapy. Understanding the natural history of skin health and disease in BBS provides valuable insight in the therapeutic setting of enhanced melanocortin stimulation. Improved understanding of the dermatologic manifestations of BBS is clearly needed to inform patients, clinicians, and researchers alike.

There are recognized limitations in this prospective, observational study. BBS is a rare disease, and the relatively small number of individuals in the cohort limits the ability to identify patterns of skin disease. The geographic dispersion of individuals with BBS creates a barrier to subject enrollment for dermatologic evaluation and longitudinal tracking of disease evolution. Comparison studies of cutaneous disorders in BBS to nonciliopathic obesity diseases would yield new insight into the role of cilia in cutaneous disease.

In conclusion, we report prospective observations of cutaneous diseases in BBS within the context of a large, multispecialty BBS clinic. Diverse skin diseases were observed in all age groups and BBS genotypes. KP was particularly common in these subjects and exceeded the prevalence observed in non-BBS obese populations, which suggests that KP may be a feature of this ciliopathy. The study, however, does not clearly differentiate the impact of systemic conditions on skin health from the underlying ciliopathy. The increased prevalence of dermatoses in our cohort suggests that patients with BBS and their caregivers may benefit from counseling on skin care and supports the importance of dermatologist involvement in the health care of individuals with BBS.

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