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RESEARCH ARTICLE

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Trends in pulmonary function in patients with Birt-Hogg-Dubé syndrome: a retrospective cohort study

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ABSTRACT

Background: Birt-Hogg-Dubé syndrome (BHD), a rare genetic disease characterized by multiple pulmonary cysts, can lead to spontaneous pneumothorax, cutaneous hamartomas, renal cysts, and renal cell cancer. The overall aim of this study was to assess clinical characteristics of patients with BHD-emphasizing on trends in pulmonary function patterns.

Methods: By use of data from electronic patient journals, we conducted a retrospective cohort study on clinical characteristics and pulmonary function tests (PFT) from patients with BHD, who were clinically followed-up in a Danish tertiary referral center for rare and interstitial lung diseases.

Results: A total of 101 patients (44 men (43.6%); mean age 48.4 years (SD ± 15.9 years)) with BHD were included. Chest HRCT scans revealed pulmonary cysts in 82.2% of whom 38.6% had experienced at least one pneumothorax (median 2; IQR1–4). Baseline PFT showed FEV1/FVC ratio and RV% within normal values of predicted. In 28.7% of the patients, a slight decrease in DLco below 80% of predicted was observed (mean 86.9% ± SD 15.8%). At two years follow-up, there were no significant declines in FEV1 and FVC, nor after accounting for age, gender, and smoking. At baseline cutaneous manifestations were found in 58.4% of the patients, 47.5% had benign renal cysts, and 11.9% had renal tumours.

Conclusion: More than 80% of patients with BHD presented with pulmonary cysts, but consistent with other studies all had normal PFTs at two years follow-up. We conclude that routine monitoring of pulmonary function and pulmonary follow-up may not be necessary in patients with BHD.

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Introduction

Birt-Hogg-Dubé syndrome (BHD) is a rare genetic disorder with autosomal dominant inheritance caused by germline loss-of-function pathogenic variants in the folliculin (*FLCN*) gene, located on chromosome 17, which produces folliculin [1]. BHD is characterized by multiple thin-walled pulmonary cysts which can lead to spontaneous pneumothorax, growth of cutaneous hamartomas, and renal cysts which transform into renal cell cancer (RCC) in 12% of BHD patients [2,3].

At present, approximately 400 families worldwide are reported with BHD, however, the prevalence is assumed to be underestimated due to underdiagnosis, which might be explained by incomplete penetration of clinical manifestations, large variance in expression of symptoms, and overall lack of focus on this disease entity. Precise epidemiological measures for prevalence and incidence of BHD in Denmark as well as worldwide are still unknown [3–5].

Up to 87% of individuals with BHD will develop pulmonary cysts that are generally characterized as multiple, bilateral, subpleural, lentiformed, and predominantly located in the basal parts of the lung [3,6–8]. Even with presence of multiple pulmonary cysts, BHD

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patients' lung parenchyma is only minimally affected, which is emphasized by their often normal pulmonary physiology. However, when cysts are predominant, diffusion capacity is expected to be slightly reduced [9,10]. Due to the pulmonary cysts, BHD patients possess a 50% higher likelihood of developing spontaneous pneumothorax compared to the background population, and further approximately 30% will have one or more relapses [11–14].

Information regarding pulmonary function in the form of pulmonary function test (PFT) parameters in individuals with BHD are limited and usually only investigated in small populations with cross-sectional data. This fact is further pointed out in a recent clinical practice guideline for the diagnosis, surveillance and management of BHD in which only moderate evidence for continuing PTF follow-up could be established [8,15–18]. However, a recent study by Daccord and colleagues, based on retrospective data from 96 BHD patients found a slightly increased residual volume (RV) and reduced diffusion of the lungs for carbon monoxide (DLco) compared to normal references [19]. Additionally, among 57 BHD patients observed over a median period of 2.8 years, no significant deterioration of PFT parameters such as forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) occurred. On basis of the Daccord study, the need for prolonged pulmonary follow-up for several years may not be warranted [19].

In Denmark, it is usually the departments of respiratory medicine that are responsible for following-up patients with BHD, which as standard involves a PFT and an abdominal magnetic resonance imaging (MRI) every second years, where the main purpose of this follow-up is to screen for RCC [20]. Alongside the study of Daccord, the overall impression is that pulmonary cysts associated with BHD exhibit very slow development and have a minimal effect on pulmonary function over time. However, no such long-term Danish follow-up data to explore this assertion have been available.

The overall aim for this retrospective cohort study was to assess the development of pulmonary function over time together with exploration of other major clinical characteristics in patients with BHD.

Methods

Study design, setting, and inclusion criteria

In this single-center cohort study, we retrospectively collected data on BHD patients who were clinically followed at South Danish Center for Interstitial Lung Diseases (SCILS), a tertiary referral center for interstitial and rare lung diseases, at Odense University Hospital, Denmark, from January 2018 to May 2023. At baseline, all BHD patients had an abdominal MRI, a chest high-resolution computed tomography (HRCT), a PFT, and an *FLCN* analysis performed. The patients received genetic counselling at, Department of Clinical Genetics and were introduced to the follow-up programme by Center for Rare and Complex Diseases (CAKS). Follow-up was conducted every second year at SCILS, and as default included a PFT and MRI scan of the kidneys. Patients were included with a diagnosis of BHD corresponding to the diagnostic criteria proposed by Menko et al. [2].

Data collection

Data on different clinical characteristics of patients with BHD were collected from electronic patient journals (Table 1). A PFT was performed according to guidelines of the European Respiratory Society (ERS) and American Thoracic Society (ATS) [21], and included measurements of FEV_1, and forced FVC in liters and as percentages of predicted (% pred.) as well as FEV_1/FVC ratio, total lung capacity (TLC), residual volume (RV), RV/TLC, DLco, and carbon monoxide transfer coefficient assessed on basis of alveolar volume (V_A) expressed as DLco/V_A and adjusted for hemoglobin. The ERS official technical standard was used to calculate all predicted values [21].

Data analysis

Continuous variables are presented as data with mean ± standard deviation (SD) if normally distributed. Non-normally distributed variables are presented as medians with interquartile ranges (IQR). Normality was assessed visually and using Shapiro-Wilk test. Categorical data are presented as absolute numbers and percentages.

Multivariate linear regression was used to analyse the associations between respiratory function at follow-up and the variables age, gender, smoking, and baseline respiratory function at follow-up. Patients without a follow-up date 2 years (±3 months) after baseline were excluded from this analysis. Paired t-test for the mean difference in respiratory function from baseline to follow-up was conducted, including 95% confidence intervals. Sensitivity analysis excluding patients with pleurodesis was conducted for both multivariate linear regression and paired t-test. A p-value <0.05 was considered statistically significant. Analyses were performed using Stata/BE 17 (StataCorp, College Station, TX, USA).

Table 1. Clinical characteristics in 101 BHD patients.

	Study sample ($n = 101$)
Diagnosis by FLCN gene mutation, n (%)	101 (100.0)
Diagnosis by combination of other criteria, n (%)	0 (0.0)
Age at diagnosis, mean (SD)	48.4 (15.9)
Men	*47.2 (15.7)*
Women	*49.3 (16.1)*
Male sex, n (%)	44 (43.6)
Never-smokers, n (%)	51 (50.5)
Men	*24 (47.1)*
Women	*27 (52.9)*
Active smokers, n (%)	21 (20.8)
Men	*7 (33.3)*
Women	*14 (66.7)*
Former smokers, n (%)	29 (28.7)
Men	*13 (44.8)*
Women	*16 (55.2)*
Pack years (former and active smokers), median (IQR)	16.5 [8.8–23.5]
Missing	*22 (44.0)*
Pulmonary cyst on HRCT, n (%)	83 (82.2)
1–5 cysts	*16 (19.3)*
6–10 cysts	*17 (20.5)*
11+ cysts	*50 (60.2)*
Cutaneous manifestations, n (%)	59 (58.4)
On face	*35 (59.3)*
Neck	*3 (5.1)*
Behind ear	*1 (1.7)*
Upper body	*2 (3.4)*
Combination	*17 (28.8)*
Other	*1 (1.7)*
Renal cell carcinoma, n (%)	12 (11.9)
Benign renal cyst, n (%)	*48 (47.5)*
1–5 cysts	*26 (25.7)*
6–10 cysts	*7 (6.9)*
11+ cysts	*15 (14.9)*
Renal cyst unilateral/bilateral, n (%)	17 (16.8)/31 (30.7)
Familial history of pneumothorax, n (%)	78 (77.2)
Missing	4 (4.0)
Dyspnea, n (%)	6 (5.9)
Cough, n (%)	3 (3.0)
Expectorate, n (%)	0 (0.0)
Hemooptysis, n (%)	1 (1.0)
Pneumothorax (≥1), n (%)	39 (38.6)
Men with PTX, n (%)	*20 (51.3)*
Age in men with PTX, mean (SD)	*30.8 (12.8)*
Missing age in men with PTX, n (%)	*5 (25.0)*
Women with PTX, n (%)	*19 (48.7)*
Mean age in women with PTX, mean (SD)	*40.3 (11.2)*
Missing age in women with PTX, n (%)	*3 (15.8)*
Number of pneumothoraxes, median (IQR)	2.0 [1.0–4.0]
Pleurodesis, n (%)	16 (15.8)

HRCT high-resolution computed tomography, PTX pneumothorax. Data are presented as n (%), mean (standard deviation) or median (interquartile range), unless otherwise stated.

Results

Patient characteristics

Patient characteristics and demographics of the 101 patients with BHD are presented in Table 1. All 101 patients had a confirmed pathogenic variant in FLCN, and thus all fulfilled one of the major criteria for obtaining the BHD diagnosis. The mean age at diagnosis was 48.4 (SD±15.9) years, and 57 (56.4%) were female. Nearly half of the patients were either active ($n = 21$) or former ($n = 29$) smokers with a median of 16.5 pack-years (IQR 8.8–23.5). HRCT scans revealed pulmonary cysts in 83 patients (82.2%) of whom 50 patients (60.2%) had more than 11 cysts (Figure 1). In total 39 patients (38.6%) experienced at least one pneumothorax, with a median occurrence of two per patient (IQR 1–4). Pleurodesis was performed in 16 patients (15.8%) Cutaneous manifestations and benign renal cysts were present in 59 (58.4%) and 48 (47.5%) of the patients, respectively, and one out of eight (11.9%) had developed malignant renal tumours.

Pulmonary function at baseline

The majority of patients had pulmonary function parameters (expressed as % of predicted) within the normal ranges as shown in Table 2. In 29 patients (28.7%), a DLco % predicted was found to be below normal values, and only 3 patients (3%) had RV values exceeding 120% predicted.

Pulmonary function during follow-up

The planned follow-up period spanned over a period of 2 years ±3 months. Patients who did not have a follow-up scheduled within this time frame were excluded from the analysis ($n = 70$) resulting in 31 patients fulfilling the definition for follow-up analysis. RV and TLC were not available at follow-up. When adjusted for age, gender, and smoking, the multivariate linear regression analysis found that age was significantly associated with lower FEV_1 ($\beta = -0.32$; $p = 0.016$) and lower FEV_1/FVC ($\beta = -0.17$; $p = 0.013$). Former smoking was found to be associated with significantly higher FEV_1 ($\beta = -9.55$; $p = 0.026$), while no association with decreased FEV1 was observed for current smoking. Detailed results can be found in Table 3.

When comparing the follow-up measurements of FEV_1 and FVC in litres to the baseline values, no statistically significant differences were found over time as indicated in Table 4. The sensitivity analysis excluding patients with pleurodesis as well as the sensitivity analysis excluding pneumothorax did not change the patterns found in both the multivariate linear regression analysis, and the paired t-test analysis (Supplementary tables 5, 6 and 7).

Discussion

The main findings from this study were that our BHD patients had normal mean pulmonary function parameters at baseline, which over a 2-year follow-up period was without significant deteriorations observed.

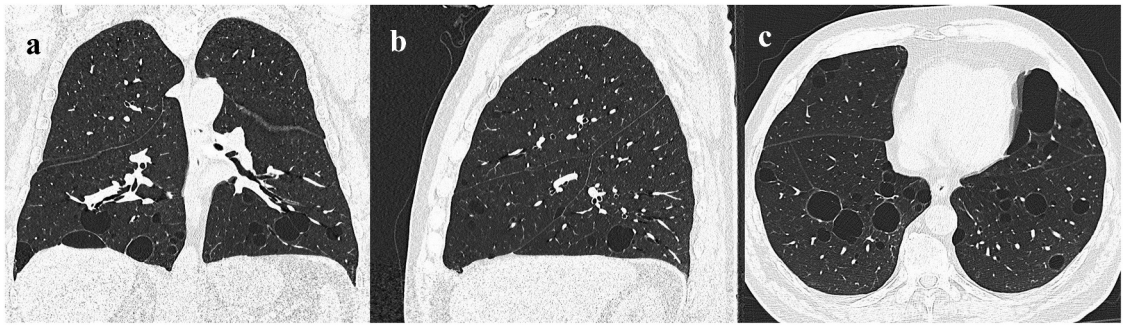

Figure 1. Patient with BHD with coronal (A), sagittal (B) and transversal (C), HRCT images showing thin-walled, round, diffuse cysts of different sizes with predominant basal distribution.

Table 2. Pulmonary function parameters at baseline.

	Mean (SD)	Abnormal values criterion	Frequency of abnormal values (%)
FEV_1 % pred[a]	97.9 (13.3)	<80	9 (8.9)
FVC % pred[a]	105.3 (14.2)	<80	5 (5.0)
FEV_1/FVC, %[a]	76.6 (7.3)	<70	13 (12.9)
TLC % pred[b]	99.1 (13.0)	<80/> 120	3 (3.0)/1 (1.0)
RV % pred[b]	99.3 (28.3)	>120	3 (3.0)
RV/TLC % pred[b]	95.1 (21.2)	>120	2 (2.0)
DLco % pred[c]	86.9 (15.8)	<80	29 (28.7)
$DLco/V_A$ pred[c]	95.0 (16.7)	<80	16 (15.8)

FEV_1 forced expiratory volume in one second, FVC forced vital capacity, TLC total lung capacity, RV residual volume, DLco carbon monoxide transfer factor, $DLco/V_A$ carbon monoxide transfer coefficient. Data are presented as n (%) or mean (standard deviation) unless otherwise stated. [a]98 patients (97.0%) with available baseline pulmonary function measure, [b]28 patients (27.7%) with available baseline pulmonary function measure [c]93 patients (92.1%) with available baseline pulmonary function measure.

Table 3. Multivariate linear regression analysis of the associations between clinical characteristics and follow-up pulmonary function.

	FEV_1 % pred[a]	FVC % pred[a]	FEV_1/FVC[a]	DLco % pred[b]	$DLco/V_A$ pred[b]
Age	−0.32; **0.016**	−0.17; 0.332	−0.17; **0.013**	0.17; 0.638	0.28; 0.484
Male	−0.87; 0.794	1.76; 0.706	−1.01; 0.500	18.57; 0.170	20.07; 0.144
Former smoker	9.55; **0.026**	8.77; 0.153	1.48; 0.427	11.85; 0.401	19.22; 0.297
Smoker	−0.62; 0.869	−2.48; 0.646	0.33; 0.850	26.89: 0.095	30.05; 0.094
Baseline PFT	0.69; <0.001	0.68; <0.001	0.86; <0.001	1.09; 0.019	1.20; 0.009
R-squared	0.71	0.55	0.73	0.62	0.64

FEV_1 forced expiratory volume in one second, FVC forced vital capacity, DLco carbon monoxide transfer factor, $DLco/V_A$ carbon monoxide transfer coefficient. All data for exposures are coefficient; p-value. R-squared is the goodness-of-fit measure for each linear regression model. [a]31 patients with available data at follow-up 2 years (±3 months) after baseline. [b]18 patients with available data.

Table 4. Paired t-test with pulmonary function at baseline vs at follow-up.

	Baseline	Follow-up	Difference	p-value
FEV_1 (liters)	3.25 (2.87–3.64)	3.13 (2.77–3.49)	−0.12 (−0.25–0.003)	0.0549
FVC (liters)	4.21 (3.76–4.65)	4.16 (3.70–4.61)	−0.05 (−0.27–0.17)	0.6510

FEV_1 forced expiratory volume in one second, FVC forced vital capacity. Paired t-test with respective pulmonary function measure at baseline vs at follow-up as outcome. Data are mean and (95% CI) unless otherwise stated.

The only significant clinical variable associated with decline in pulmonary function as measured by FEV_1 was age, which was expected as a result of a natural age-related loss of pulmonary function. Previous smoking was slightly associated with increasing FEV_1 and was unaffected by pleurodesis. No other relevant statistically significant associations between pulmonary physiology variables and clinical characteristics were identified. Our cohort only had a minor degree of respiratory symptoms as cough and dyspnoea. To our knowledge, this study reports clinical characteristics and trends in pulmonary function of BHD-patients from one of the largest described BHD cohorts, however, exceeded by the proportion of follow-up patients ($n = 57$) in the study from Daccord and colleagues, where also the follow-up time was slightly longer than in our study. Daccord and colleagues explored 96 patients, with BHD according to trends in lung

function and found an equal gender distribution and normal PFT values at baseline. To compare results from their study with our study, we chose to examine the same baseline characteristics, and likewise included smoking status as a well-known confounder to influence PFT measurements. As such, together with Daccord and colleagues, our study contribute with further evidence that PFT may not be required in respiratory almost asymptomatic patients with BHD [19].

Our study revealed a slight reduction in DLco % predicted at baseline with 29 patients (28.7%) presenting with a value below the predicted 80% DLco. This decrease in DLco may be attributed to a significant number of pulmonary cysts in BHD patients supported by observations that 83 patients (82.2%) had pulmonary cysts, among whom more than 50 patients (60.2%) had more than 11 cysts. While the lung parenchyma is generally minimally affected by these cysts, they could potentially lead to a loss of alveolar units available for efficient gas exchange. This may account for the lower DLco values observed in our study population [10]. Another explanation could be that repeatable pneumothoraxes over time could be a driving factor for the trend in DLco decline; however, sensitivity analyses excluding patients with previous pneumothorax, confirmed our main findings. The consistency of the results and effect sizes between the main- and sensitivity analyses allows us to confidently rely on the main regression results, without concerns that pneumothorax might have influenced our conclusion.

A significant association was only observed between former smoking and increasing FEV_1, while no statistically significant effect was found for other PFT parameters. The limited size of the follow-up group and the relatively short duration of follow-up may have contributed to these findings. Additionally, the relatively young age of the participants and the lower median pack years of smoking could provide further explanations for the absence of significant effects on pulmonary function.

When performing sensitivity analysis excluding patients with pleurodesis, no substantial changes were observed in the results of PFT parameters, as the significant confounders remained unchanged. There was a marginal improvement in the R-squared value for FVC, which increased from 55% to 61%. However, this indicates that the model did not exhibit a significantly improved fit following the sensitivity analysis. This outcome could potentially be attributed to the limited number of follow-up patients with pleurodesis in combination with the overall small size of the follow-up cohort.

Daccord et al. conducted a study with a population similar to ours on 96 patients with BHD. The mean age at diagnosis was reported as 48 ± 14 years among whom 46 patients (48%) were female, and of whom 49 patients (51%) were either active or former smokers, having a mean pack-year history of 14 ± 10 [19]. In their study, Daccord et al. observed minor abnormalities in baseline measurements for RV and DLco. RV was slightly increased with a mean value of 116 ± 36% predicted, while DLco was slightly reduced, with a mean value of 85 ± 18% predicted. They found that in 28 patients (41%) the RV values exceeded 120% predicted, and 23 patients (33%) had DLco values below 80% predicted, while no significant abnormalities were noticed in other pulmonary function parameters. In our study, we did not identify significant abnormalities in RV, but a similar decrease in DLco was observed. The mean RV value in our study was 99.3 ± 28.3, with only 3% of patients showing abnormal values. However, it is important to emphasize that the discrepancy between observations in these two studies may be explained by sample size as we only had data available for RV in 28 patients, contrary to Daccord et al., who included baseline RV data from 69 patients. Similar to our findings, the Daccord study revealed with a mean follow-up duration of 2.8 years (SD ±3.5 years) that BHD did not have a significant impact on trends in pulmonary function, based on data from 57 patients [19]. This tendency was also observed in a recent minor follow-up study by Cho et al. who neither found any statistically significant changes in PFT patterns. Nevertheless, when using a linear mixed model decreasing time trends for PFT values were observed; however, this model was based on a lower follow-up time of only 6 months and without confounder adjustment. In such, one may speculate whether the mixed models findings from the study are clinical representative [22].

The prevalence of other major clinical characteristics considered in this study closely aligns with a recent investigation on the prevalence of BHD conducted by Bruinsma et al. [3]. In their systematic review, Bruinsma et al. reported a prevalence of 15.2% for renal tumours, 81.3% for pulmonary cysts, and 47.1% for cutaneous manifestations. Our findings indicate a slightly lower prevalence of RCC of 11.9%, similar to 82.2% for pulmonary cysts, and a slightly higher prevalence of 58.4% for cutaneous manifestations. However, comparing results across studies is challenging and not always meaningful due to heterogeneous approaches referring to different health care setups and referral patterns, inclusion criteria, disease criteria definitions, and the nature of the studies.

This study has several limitations that should be considered when interpreting the findings. The retrospective design and the small sample size at follow-up may limit the generalizability. The number of patients at follow-up was smaller than expected before the study began. This is likely due to the COVID-19 pandemic restrictions causing a large number of patients to skip their PFT at follow-up. However, as all patients were diagnosed through genetic testing, and in this way having excluded patients fulfilling criteria for BHD without a verified genetic disposition, selection bias according to diagnosis is expected to be marginal. Fluctuations in performance of PFT are expected despite these tests are conducted at the same hospital. The analysis focused only on age, gender, and smoking as potential confounders associated with pulmonary function decline, excluding other potential factors such as pulmonary cyst count and genetic variants present. Whether the inclusion of these potential confounders may have altered our findings is questionable and requires further investigation. For more comprehensive insights on BHD and its development over time, future studies should prioritize an extended follow-up duration with a larger sample size obtained through multicenter involvement. Additionally, including additional confounders such as genetic variants or pulmonary cyst count may further enhance the understanding of the BHD.

The strengths of the present study are the careful registration of all patients in CAKS and that it has been possible to read every file of the patients. By this manner, it has been possible to register every treatment which was offered to the patients.

Conclusion

More than eight out of ten patients with BHD presented with pulmonary cysts, however, all had normal pulmonary function parameters at two years follow-up without any significant deterioration in pulmonary function. Consistent with other studies this suggests that routine monitoring of pulmonary function may not be warranted in BHD follow-up. Future studies on genetic profiles should explore whether certain BHD genotypes differ from others according to affection of pulmonary function.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

According to Danish law, no ethical approval is needed for retrospective studies performed on medical records during the past 5 years. In addition, the Danish Data Protection Agency (J no. 22/47359) approved the study. All patients gave written informed consent.

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