Review Article

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# Birt-Hogg-Dubé Syndrome: A Narrative Review of Clinical Spectrum, Molecular Pathogenesis, and Multisystem Management Strategies

Surgery Section

SHAILABH[1], IMRAN ALI KHAN[2], ANUP ZADE[3], BHAGYESH SAPKALE[4]



## ABSTRACT

Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant rare disease with variable manifestations in the skin, lungs, and the kidneys, as a result of germline mutations in the Folliculin (FLCN) gene. It has a clinical presentation that includes fibrofolliculoma, trichodiscomas, acrochordons, pulmonary cysts with recurrent Spontaneous Pneumothorax (SP) as well as multifocal renal tumours including hybrid oncocytic, chromophobe, and clear cell carcinomas. FLCN inactivation, interference with mTOR, and AMPK signalling play a role in pathogenesis and provide tissue-specific abnormalities. Diagnosis is mostly based on clinical criteria, radiologic, skin biopsy and molecular confirmation with Next-Generation Sequencing (NGS) enhancing early detection. Treatment of BHD is organ-specific, so skin lesions are managed with dermatological surgeries, pulmonary cases are managed with Video-Assisted Thoracoscopic Surgery (VATS) or pleurodesis, nephron-sparing surgery, ablation, or surveillance of tumours are used in the cases involving the kidneys. Lifelong follow-up is suggested because of the risk of tumour recurrence in many such cases of BHD. On early identification, proper treatment, and organised monitoring, the patients with BHD syndrome will be able to lead a nearly normal life, which stresses the need to use multidisciplinary care to reduce morbidity and increase the prospects of long-term outcomes.

**Keywords:** Acrochordons, Fibrofolliculomas, Pulmonary cysts, Renal tumours, Spontaneous pneumothorax

## INTRODUCTION

The BHD syndrome is a rare autosomal dominant disease that was first described in 1977 by BHD who reported families with hereditary multiple fibrofolliculomas, trichodiscomas and acrochordons [1]. The causative gene, Folliculin (FLCN) was discovered in 2002; mutation in this tumour suppressor gene causes the range of clinical features observed in BHD [1]. BHD presents clinically with skin lesions, pulmonary cysts, recurrent SP and benign or malignant renal tumours [2]. Skin findings are highly variable, even within families, but cause morbidity with lung and kidney manifestations, though the phenotypic expression remains very variable, even in adulthood [1,2]. A study based on the Bayes' theorem, applied to published data on SP incidence, SP recurrence in BHD, and the proportion of SP patients with BHD, approximated a prevalence rate of approximately 1.86 cases/million (95% CI 1.16-3.00/million), and that there was no significant difference between male and female [3]. Over 600 families with BHD have been reported across the world, but under diagnosis is probable because of inconsistent expressivity and awareness [3]. There is a rather high-risk of SP in BHD patients, it is estimated that no less than 43 percent of individuals with BHD have at least one SP [3]. The given article about BHD syndrome, aims to highlight its clinical presentation, pathophysiology, and diagnosis. It also examines the existing management methods of the affected organ systems, such as skin, lungs, and kidneys. Lastly, the article identifies prognostic factors and the significance of multidisciplinary care in maximising the outcome in BHD patients.

### Symptoms of Birt-Hogg-Dubé (BHD) Syndrome

The BHD syndrome is a disorder with clear clinical presentations in the skin, lungs, and kidneys [4]. Some of the first and most common cutaneous manifestations, such as fibrofolliculomas (benign papules that develop within hair follicles), trichodiscomas, acrochordons (skin tags), oral papules, cutaneous collagenomas and epidermal cysts [4]. These skin lesions are usually initiated between 2nd to 4th decades of life and are normally observed to increase in size and number as a person grows older [5]. Another characteristic is pulmonary involvement where majority of the patients develop numerous bilateral lung cysts, mostly in the basal areas [4]. Although the majority of them are asymptomatic, a large percentage of them develop into recurrent SP and result in respiratory morbidity [6]. The renal presentation is characterised by the presence of simple renal cysts as well as multifocal and bilateral renal tumours with hybrid oncocytic tumour, chromophobe Renal Cell Carcinoma (RCC) and clear cell carcinoma being the most frequent histologic variants [5,6]. Less quantified but possible complications include cosmetic disfigurement by lesions in the skin, and risks associated with recurrent nature of pneumothorases (e.g., respiratory compromise) [6]. Spectrum of signs, symptoms, and complications in BHD syndrome are mentioned in [Table/Fig-1] [4-6].

### Pathogenesis and Molecular Mechanisms of Birt-Hogg-Dubé (BHD) Syndrome

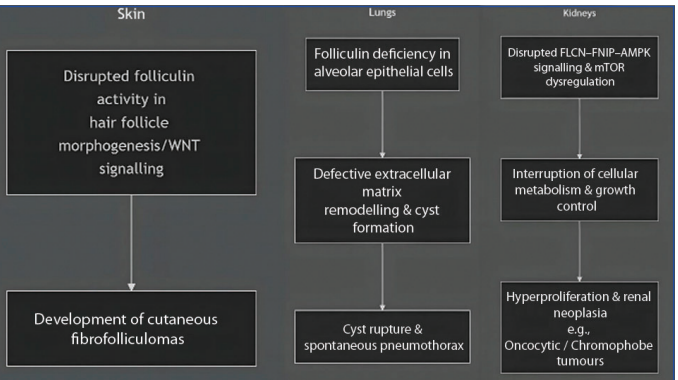
The BHD syndrome is the result of germline like mutations of the FLCN gene that is situated on the chromosome 17p11.2 [7]. These mutations are usually frameshift, nonsense or splice-site mutations that cause a loss of the functionality of FLCN [7]. The second (wildtype) allele of FLCN is somatically inactivated (by mutation or loss of chromosomes) in most of the kidney tumours that are linked to BHD, and is a common tumour suppressor paradigm [7]. Folliculin binds to Folliculin-interacting proteins FNIP1 and FNIP2 with the cellular energy sensor (AMPK), and regulates signalling through the mTOR pathway; and in non-functional FLCN these interactions are disrupted [8].

Loss of normal regulatory activity of the FLCN gene leads to downstream effects in multiple tissues, resulting in the characteristic phenotypic triad of cutaneous fibrofolliculomas, pulmonary cysts with a predisposition to spontaneous pneumothorax, and renal neoplasms [9]. For example, cellular metabolism, mitochondrial

| System involved | Signs and symptoms | Complications |
|---|---|---|
| Skin [4,5] | - Fibrofolliculomas (benign papules from hair follicles)<br>- Trichodiscomas<br>- Acrochordons (skin tags)<br>- Oral papules<br>- Cutaneous collagenomas<br>- Epidermal cysts<br>Onset: 2nd-4th decade; increase in size and number with age | - Cosmetic disfigurement due to visible lesions |
| Lungs [4,6] | - Multiple bilateral lung cysts (predominantly basal)<br>- Often asymptomatic | - Recurrent Spontaneous Pneumothorax (SP)<br>- Respiratory morbidity (e.g., compromise from recurrent SP) |
| Kidneys [5,6] | - Simple renal cysts<br>- Multifocal and bilateral renal tumours<br>- Histologic variants: hybrid oncocytic tumours, chromophobe RCC, clear cell RCC | - RCC (increased lifetime risk)<br>- Potential renal dysfunction or metastasis |

**[Table/Fig-1]:** Spectrum of signs, symptoms, and complications in Birt-Hogg-Dubé (BHD) syndrome [4-6].
SP: Spontaneous pneumothorax; RCC: Renal cell carcinoma

oxidative phosphorylation and mTORC1-driven cell growth are interrupted by FLCN-FNIP signalling in the kidneys, resulting in hyperproliferation and neoplasm growth, especially of the hybrid oncocytic/chromophobe types [8,9]. Folliculin deficiency in lung tissue causes defects in alveolar epithelial cell (particularly type I pneumocytes) or extracellular matrix remodelling that facilitates the development of cysts; these cysts can rupture causing pneumothorax [8]. The skin lesions (fibrofolliculomas) are the product of the folliculin activity in hair follicle morphogenesis, and possibly WNT signalling, but the exact molecular processes involved in this case are less well characterised [8,10]. Tissue-specific pathogenesis of BHD syndrome is described through [Table/Fig-2].




**[Table/Fig-2]:** Tissue-specific pathogenesis of Birt-Hogg-Dubé (BHD) syndrome.
Figure is created by authors

## Diagnosis and Emerging Diagnostic Approaches in Birt-Hogg-Dubé (BHD) Syndrome

The clinical, radiologic, histopathologic, and molecular findings are used in the diagnosis of BHD syndrome [11]. A proper final diagnosis is made upon the occurrence of either one major criterion (at least five fibrofolliculomas or trichodiscomas with at least one proven by biopsy, or a pathogenic mutation of FLCN) or two minor criterias [11,12]. Minor criteria include multiple lung cysts with or without SP, early-onset (<50 years), multifocal, or bilateral renal cancer, or a first-degree relative with BHD [12]. The FLCN gene molecular testing is considered the gold standard, as the majority of the affected patients carry truncating or splice-site mutations, but a small proportion of cases (7 to 9 percent only) have intragenic large-scale rearrangements that can be detected using copy-number assays [12]. The suspected cases can be confirmed through dermatologic examination with skin biopsy, high-resolution chest Computed Tomography (CT) to infer the typical presence of basal lung cysts, and renal examination to detect multifocal and bilateral tumours [13]. Collectively, the resulting tools enable the early detection, and genetic confirmation helps to be certain about the diagnosis and conduct cascade testing on the at-risk family members [12,13].

Recent developments in the diagnosis of BHD are about the use of NGS along with more accurate radiologic quantification to diagnose patients earlier [14]. An example a study of patients with typical lung cysts used an NGS panel and identified FLCN mutations in 35.5% of them, including three new variants; further, this study came up with a prediction model based on the number of lung cysts (>40), cyst size (>2 cm), and age, without depending on skin or kidney findings [14]. Glycoprotein Non-Metastatic B (GPNMB) expression is another emerging histopathologic marker that has been observed in eosinophilic renal tumours of confirmed FLCN mutations; this can be used to differentiate FLCN-associated renal tumours e.g., hybrid oncocytic/chromophobe tumours versus sporadic analogues [15]. In lung imaging, more detailed analysis of CT features (e.g., distribution, size and number of lung cysts) is also contributing to improved risk stratification, in part reducing the need for invasive lung biopsies in patients with compatible genotype or family history [14,16].

## Treatment Modalities for Multisystem Involvement in Birt-Hogg-Dubé (BHD) Syndrome

Skin lesions can be treated, mainly for cosmetic reasons, using dermatologic surgical approaches such as shave excision, punch excision, laser ablation, dermabrasion or electrosurgery [17,18]. Electrosurgery (with or without curettage) of the skin was relatively well tolerated and showed somewhat reduced recurrence in follow-ups (24-72 months) comparing other surgical skin-methods, and so is the most tolerable of the procedures [18]. A randomised split-face, double-blind, trial of topical rapamycin {an mechanistic Target of Rapamycin (mTOR) inhibitor} did not provide any benefit for established fibrofolliculoma [19]. Pulmonary manifestations are managed through regular surveillance and timely intervention for complications. In cases where patients develop SP, management follows the same principles as in non–BHD patients. (e.g., chest tube, possibly surgery) [20,21]. Minimally invasive surgical tools such as Video-Assisted Thoracoscopic Surgery (VATS) are used for resection of blebs or bullae and performing pleurodesis (or partial pleurectomy) in order to manage and prevent recurrent pneumothoraces [20]. There is also emphasis on patient education (symptom awareness), avoidance of risk factors (such as smoking), vaccination (e.g., influenza, pneumococcal), and imaging surveillance of lung status especially for cysts [22].

One of the more serious morbidities is the renal tumours [17]. Treatment is as per standard oncologic principles modified as per risk of BHD: small renal tumours (less than 1-3 cm depending on the guidelines) could be observed with a periodic imaging [23]. Partial nephrectomy (also known as nephron-sparing surgery) is a technique applied where possible particularly for tumours that exceed a size limit of 3 cm [24,25]. This assists in maintaining the renal functions as patients are likely to have various renal tumours throughout lifetime [25]. Radical nephrectomy (removal of the entire kidney) can be done in certain situations, as partial removal is either not possible (location of tumour), or possible but very large or spread over multiple areas [26]. Staged surgery applies in those patients that have bilateral large tumours: one side is first operated (usually the side for partial nephrectomy), and then the other [25,26]. The guidelines suggest lifelong follow-up since the early adulthood (age around 20) years, with Magnetic Resonance Imaging (MRI) or contrast CT as possible [25]. Percutaneous thermal ablation encompassing both radiofrequency and the cryoablation has developed to be a less invasive procedure in comparison to surgery as an option in BHD patients with RCC [27]. Surgical and medical management of BHD syndrome is described in [Table/Fig-3] [17-27].

| System/ manifestation | Treatment/management | Notes/ comments | References |
|---|---|---|---|
| Skin lesions (e.g., fibrofolliculomas, trichodiscomas) | - Shave excision<br>- Punch excision<br>- Laser ablation<br>- Dermabrasion<br>- Electrosurgery (± curettage) | Electrosurgery showed best tolerability and lower recurrence (24–72 months). Randomised trial: topical rapamycin (mTOR inhibitor) not effective. | [17-19]. |
| Pulmonary manifestations (lung cysts, Spontaneous Pneumothorax) | - Standard pneumothorax treatment: chest tube, possible surgery<br>- VATS for bleb/bulla resection and pleurodesis/ partial pleurectomy<br>- Preventive measures: smoking cessation, vaccinations (influenza, pneumococcal)<br>- Imaging surveillance | Patient education and symptom awareness essential. Imaging to monitor lung cysts. | [20-22]. |
| Renal tumours (oncocytomas, chromophobe RCC, hybrid oncocytic/ chromophobe tumours) | - Active surveillance: small tumours (<1–3 cm) with periodic imaging<br>- Partial nephrectomy (preferred for tumours >3 cm; nephron-sparing)<br>- Radical nephrectomy if partial not feasible (location, size, multiple spread)<br>- Staged surgery: for bilateral large tumours (one kidney operated first, then other)<br>- Percutaneous thermal ablation (radiofrequency or cryoablation) as less invasive alternative | Lifelong follow-up starting ~20 years of age. Surveillance with MRI or contrast CT. Nephron-sparing prioritised due to lifetime tumour risk. | [23-27]. |

**[Table/Fig-3]:** Surgical and medical management of Birt-Hogg-Dubé (BHD) syndrome [17-27].
BHD: Birt-Hogg-Dubé syndrome; RCC: Renal cell carcinoma; VATS: Video-assisted thoracoscopic surgery; mTOR: Mammalian target of rapamycin; MRI: Magnetic resonance imaging; CT: Computed tomography; RFA: Radiofrequency ablation

### Life Expectancy and Prognostic Factors in Birt-Hogg-Dubé (BHD) Syndrome

Life expectancy in BHD syndrome is also mostly good in cases where the patients are closely monitored since the occurrence of RCC is the major cause of mortality [28]. Renal tumours are found in a high number of patients, which is multifocal and histologically diverse, and the lifetime risk is estimated between 15-30% [28]. Aggressive or metastatic tumours are rare, but they constitute the significant cause of death [28]. Diagnosis at an early stage by periodic examination, ideally MRI minimise radiation exposure, and early surgery nephron sparing have a significant beneficial effect on the long-term results and recovery of the integrity of kidney functions [28]. Although pneumothorases do not often affect survival, they are many times recurrent and cause much of hospitalisation and loss of quality of life; prophylactic measures like pleurodesis can mitigate the recurrence [29]. Cutaneous lesions, though characteristic remains a cosmetic issue only without having a prognostic impact [30]. Renal tumour burden, compliance with surveillance measures, and pulmonary complications management are therefore prognoses that pose the strongest influence [31]. BHD can be treated with structured follow-up in special centres, which allows leading to a close-to-normal life expectancy in most affected patients [30,31].

## CONCLUSION(S)

The BHD syndrome is an uncommon autosomal dominant disease, which is known to have a triad of cutaneous lesions, pulmonary cysts with recurrent pneumothorax, and renal tumours. Its unstable phenotypic manifestation requires close clinical, radiologic, histopathologic, and molecular analysis, and the diagnosis of this disease is the gold standard FLCN gene analysis. Management is tailored according to organ involvement and includes cosmetic procedures for cutaneous lesions, appropriate surgical management for pneumothorax, and nephron-sparing surgery or ablative therapies for renal tumours. Early diagnosis, organised surveillance, and proper interventions will allow patients to have an almost normal life expectancy while minimising morbidity from renal and pulmonary complications.

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**PARTICULARS OF CONTRIBUTORS:**
1. Junior Resident, Department of General Surgery, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
2. Professor, Department of General Surgery, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
3. Associate Professor, Department of General Surgery, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
4. Undergraduate Student, Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**
Dr. Shailabh,
Junior Resident, Department of General Surgery, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education and Research, Wardha-442004, Maharashtra, India.
E-mail: shailabh.bhadra@gmail.com

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