

Introduction

Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant disorder caused by mutations in the *Folliculin (FLCN)* gene found on chromosome 17p11.2. It may be classified as a hamartoma syndrome. BHD syndrome is considered to be rare; the most recent estimated incidence is 1/200,000.¹

BHD syndrome is characterised by the development of fibrofolliculomas, pulmonary cysts and pneumothorax, as well as a predisposition to renal cancers. Affected individuals may show any or all of these symptoms over time.

Fibrofolliculomas



Fibrofolliculomas are benign epidermal tumours originating from hair follicles. The fibrofolliculomas associated with BHD syndrome appear as white growths on the skin of the head and upper torso. They often develop in early adulthood, and an individual may have none, one or several hundred over their lifetime. There is currently no permanent treatment, though temporary cosmetic treatments are available. A rapamycin cream is in clinical trials.

Pneumothorax

BHD syndrome leads to the development of pulmonary cysts in some individuals. These air-filled cysts, also called blebs or bullae, occur on the surface of the lung. The cysts are prone to rupture and so instigate spontaneous pneumothorax.



It has not been determined which BHD patients will experience spontaneous pneumothorax or whether certain types of activity should be contraindicated. It has been reported that BHD patients with pulmonary cysts had a 24% risk of spontaneous pneumothorax, and that following a single episode of spontaneous pneumothorax, recurrent events were more common.²

Pulmonary cysts are the earliest and most common BHD manifestation. It has been suggested that BHD syndrome should be considered for patients with multiple lung cysts, even when no other symptoms are present.³

Renal cell carcinoma



BHD syndrome is associated with the presentation of multifocal bilateral renal tumours. Chromophobe renal cell carcinoma (RCC) and hybrid chromophobe and oncocytic RCC are typical for patients with BHD syndrome (together accounting for >80% of BHD-associated RCC).⁴ However, other histological subtypes can occur, including clear-cell and papillary carcinoma.

The risk of renal cell carcinoma is considered to be around 30% for BHD patients. If tumours are present, partial nephrectomy is recommended when they reach 3cm in diameter. Current recommendation is for all BHD patients to be monitored for renal neoplasms every 1-2 years.

1. Orphanet Report Series. Prevalence of rare diseases: Bibliographic data. May 2011, Number 1. http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf.
2. Toro et al. Lung cysts, spontaneous pneumothorax, and genetic associations in 89 families with Birt-Hogg-Dubé syndrome. *Am J Respir Crit Care Med.* 2007; 175: 1044-53.
3. Hayashi et al. Birt-Hogg-Dubé syndrome with multiple cysts and recurrent pneumothorax: pathological findings. *Intern Med.* 2010;49(19):2137-42.
4. Warwick G, Izatt L, Sawicka E. Renal cancer associated with recurrent spontaneous pneumothorax in Birt-Hogg-Dubé syndrome: a case report and review of the literature. *J Med Case Reports.* 2010;4:106.