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Birt-Hogg-Dubé syndrome (BHDS): *FLCN* Mutations

Birt-Hogg-Dube syndrome, or BHDS, is an inherited condition caused by a mutation in the *FLCN* gene. Individuals with BHDS have an increased risk for a variety of cutaneous (skin) lesions, pulmonary cysts, spontaneous pneumothorax (collapsed lung), and renal tumors. The severity of symptoms as well as the presence/absence of symptoms can vary significantly among affected individuals, even within the same family.

Clinical Features and General Management Recommendations

There are no consensus guidelines for the management of individuals with Birt-Hogg Dubé syndrome (BHDS). However, the following recommendations have been proposed, based on expert opinion.[1,4,5,6]

Feature	Risk	Surveillance and Management Recommendations

Cutaneous Lesions	• Individuals with BHDS typically have multiple, small, skin-colored domed papules over their face, neck, and upper-trunk.
	  ○ Skin lesions included: fibrofolliculomas, trichodiscomas, angiofibromas, acrochordons, and perifollicular fibromas.
	  ○ Some individuals have oral papules and cutaneous collagenomas.
	  ○ Some families with germline *FLCN* mutations present with cutaneous features as their only clinical manifestation of the syndrome.
	  ○ Skin lesions can increase in size and number with age.
	• Onset: 3rd or 4th decade of life.
		Surveillance/Treatment
		• No specific treatment for typical BDH-related skin lesions.
		• Treatment of fibrofolliculomas and trichodiscomas is difficult. Laser ablation may improve the appearance of these lesions, but they can reappear over time.
		• Consider full skin exam every 6-12 months for possible risk of melanoma.

Lung Cysts and Spontaneous Pneumothorax	• Bilateral Lung Cysts: 77-89% of individuals with BHDS (asymptomatic, but high risk of developing spontaneous pneumothorax).[2] • Spontaneous Pneumothorax: 20-40% of individuals with BHDS.[3] 75% will experience a recurrent event.[5,6] The risk of spontaneous pneumothorax is increased for	*Surveillance* • Baseline high resolution computer tomography (HRCT) or CT of the chest should be performed to assess for the presence of pulmonary cysts. • There is currently no consensus on continued clinical surveillance to evaluate for the development of pulmonary cysts after baseline evaluation.[4]

	individuals with a family history of spontaneous pneumothorax.	*Agents to Avoid* • High altitudes and high ambient pressures, which may increase their risk for spontaneous pneumothorax.[4] In general, air travel is considered safe, however, it has been suggested that individuals not board an airplane with unexpected chest pain or shortness of breath. Individuals are advised against scuba diving.[5]

Renal Tumors	• 7-fold risk to develop renal tumor for individual with BHDS.
	  ○ Individuals typically have bilateral, multifocal and slow growing renal tumors.
	  ○ Most common type of renal tumor: hybrid oncocytoma and chromophobe histologic cell types or "oncocytic hybrid tumors" (67%).
	  ○ Other renal tumors: renal oncocytoma (3%), chromophobe renal cell carcinoma (23%), and a minority of clear cell renal cell carcinoma and papillary renal cell carcinoma.[1,5,6]
	• Median age of diagnosis: 48 years old.
		Surveillance
		• Annual abdominal/pelvic CT scan with contrast or MRI starting at age 20 years. Consider screening earlier if there is a family history of renal cancer before age 30.[4]
		• Renal ultrasound may also be helpful to distinguish cystic from solid renal lesions.
		• If normal at baseline, abdominal/pelvic CT scan with contrast or MRI every 2 to 3 years are the optimal studies for complete assessment of kidney lesions. However, as a result of the low aggressiveness of renal tumors in BHDS, renal ultrasound for screening individuals with BHDS may be adequate in some patients.
		  ○ The use of renal ultrasound is thought to be particularly applicable to individuals who have had 2 normal CT examinations and individuals without a family history of renal cancer.
		• If any suspicious lesion (<1.0 cm in diameter, indeterminate lesion, or complex cysts) is noted on an examination, annual abdominal/pelvic CT with contrast alternating every other year with renal MRI or abdominal ultrasound examination is recommended.
		• Tumors less than 3.0 cm in diameter may be managed by periodic imaging as they may not require surgical intervention when small.
		• Rapidly growing lesions or individuals who experience symptoms such as pain, blood in the urine, or atypical presentations may require a more individualized approach.

		• All renal lesions should be evaluated by a urologic surgeon. *Surgery* • Nephron-sparing surgery is the treatment of choice for renal tumors depending on the size and location of the tumors. Total nephrectomy may be necessary in some cases. • The main objective is to preserve as much of the kidney as possible to help preserve long-term kidney function because affected individuals typically develop multifocal and bilateral kidney tumors. *Agents to Avoid* • Cigarette smoking, as this has a strong positive correlation with renal cell carcinoma development.

Other Cancer Risks: There may be other cancer risks associated with *FLCN* mutations for which we do not yet have sufficient evidence to warrant intervention, including parotid (salivary) gland, thyroid, and colon cancers. Further research is needed to make conclusions about these cancer risks.[4]

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *FLCN* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

References

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