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Birt Hogg Dube Syndrome

Authors

Jonathan S. Crane[1]; Veronica Rutt[2]; Amanda M. Oakley[3].

Affiliations

[1] Sampson Regional Med Ctr / Campbell Univ
[2] Philadelphia College of Osteopathic Medicine
[3] University of Auckland

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Continuing Education Activity

Birt Hogg Dube syndrome is an autosomal dominant genodermatosis, usually manifesting in the third decade of life with multiple fibrofolliculomas, trichodiscomas, and acrochordons. Patients with this syndrome have an increased susceptibility to develop renal cell carcinoma, lung cysts, and spontaneous pneumothorax. This activity describes the etiology, pathophysiology, histology, evaluation, and management of patients with Birt Hogg Dube syndrome. It emphasizes the role of the interprofessional team in improving the outcome of affected patients.

Objectives:

- Describe the genetics, epidemiology, and pathophysiology of Birt Hogg Dube syndrome.
- Explain the histopathology and conditions associated with Birt Hogg Dube syndrome.
- Outline the clinical features, evaluation, and management of patients with Birt Hogg Dube syndrome.
- Explain how collaboration among interprofessional team members will improve long term outcomes when treating patients with Birt Hogg Dube syndrome.

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Introduction

Birt-Hogg-Dube syndrome (BHDS) is an autosomal dominant genodermatosis usually manifesting in the third decade of life with multiple fibrofolliculomas, trichodiscomas, and acrochordons. Patients with this syndrome have an increased susceptibility to renal cell carcinoma, lung cysts, and spontaneous pneumothorax.[1][2][3][4]

Etiology

A germline mutation of *FLCN*, which encodes the tumor-suppressor folliculin, is responsible and is located on chromosome 17p11.2. Multiple distinct mutations have been identified. Folliculin is thought to be a tumor suppressor, but its exact function is unknown. *FLCN* has been linked to the *mTOR* pathway.[5]

Epidemiology

Birt-Hogg-Dube syndrome is rare. It occurs in males and females. Patients usually present for the first time during young adult life.

Pathophysiology

Mutations lead to loss of function of folliculin. Abnormal folliculin is thought to result in the production of tumors in susceptible organs such as skin and kidney.

Histopathology

In fibrofolliculomas, there is a fibrous pink orb or amphophilic fibro mucinous orb with epithelial strands (sometimes in an anastomosing pattern) radiating outward from a central follicle-like structure. The strands of epithelium are not differentiated well enough to form hair fibers. Furthermore, the hair bulb inner or outer root sheath is not present.

History and Physical

Characteristic lesions of BHDS are described as multiple, two to four millimeters, waxy, white, dome-shaped papules that are most frequently found on the nose and cheeks. They also may be present on the ears, neck, and trunk. Expression ranges from a few localized lesions to several hundred. Histopathologically, they are benign hair follicle tumors known as trichodiscomas or fibrofolliculomas. For many years, experts have argued that fibrofolliculomas, trichodiscomas, and acrochordons in patients with BHDS may be variations of the same lesion. Trichodiscomas and fibrofolliculomas are indistinguishable on clinical examination. Some authors have shown that deeper histopathologic sections reviewed on lesions, initially called trichodiscomas, showed characteristics of fibrofolliculomas only. Furthermore, some experts argue that the proliferative epithelial components that are specific to fibrofolliculomas may only be observed in horizontal sectioning. Acrochordons, known as skin tags, are common in the general population. In BHDS, acrochordons might represent a phenotypic variant of fibrofolliculomas. Although it remains controversial, these tumors often are considered to be part of a morphological spectrum.[6][7][8][9]

Other cutaneous manifestations of BHDS include soft papules of the lips, gingiva, and buccal mucosa, connective tissue nevi, lipomas, angiolipomas, acrochordons, and facial angiofibromas. Patients with BHDS also have been found with other systemic manifestations such as medullary thyroid cancer, thyroid adenomas, parotid oncocytomas, basal lung cysts, and parathyroid adenomas. It was once thought that BHDS confers an increased development of colonic polyps and other tumors. However, studies have shown that there is no association. Given the varied expression of the syndrome, patients often may be undiagnosed. They may present with renal cancer or a spontaneous pneumothorax, both of which often occur sporadically and may not prompt physicians to look for an underlying genetic defect.

Evaluation

In 2009, Menko et al. published diagnostic criteria for BHDS. One major or two minor criteria are needed for diagnosis (Table 1). Major criteria include (1) at least five fibrofolliculomas or trichodiscomas and at least one histologically confirmed and of adult-onset, and/or (2) pathogenic *FLCN* germline mutation. Negative *FLCN* gene testing does not exclude the diagnosis as up to 40% of patients with negative testing still meet diagnostic criteria. Minor criteria include (1) multiple lung cysts, which are bilateral and basally located, (2) renal cancer before the age of 50 years, or multifocal or bilateral renal cancer, or of mixed chromophobe and oncocytic histology, and (3) a first-degree relative with BHDS. Multifocal or bilateral renal cancer with hybrid chromophobe and oncocytic histology is a hallmark of BHDS. Furthermore, the mixed pattern of chromophobe cancer and oncocytoma is typical and unique to BHDS.

Chest x-ray and high-resolution chest computed tomography (CT) scans are used to assess pulmonary cysts. Abdominal CT or magnetic resonance imaging (MRI) can be used to assess the kidneys.

Treatment / Management

Treatment for BHDS skin lesions includes destruction by electrocautery, curettage, and laser ablation, but is often followed by recurrence. Because folliculin has been implicated in the mTOR pathway, medications such as rapamycin, an mTOR inhibitor, have theoretical application in the treatment of Birt-Hogg-Dube lesions. In animal models using BHDS-condition knock-out mice, rapamycin decreased kidney pathology and increased overall survival. However, a double-blind, randomized facial left-right controlled trial in 2014 by Gijezen et al. using topical rapamycin revealed no significant difference in the treatment of fibrofolliculomas. The exact function of folliculin has yet to be elucidated.

Patients with BHDS are at increased risk of developing renal tumors lifelong, with an average age of onset at 50 years. Lifelong renal surveillance should begin at the age of twenty. Some experts recommend initial MRI followed by annual MRI or ultrasound, while others suggest CT scans every 3 to 5 years. There is also a risk for pneumothoraces, which occur in 25% of patients during the third to sixth decades. Ninety percent of adult patients will show radiographic evidence of lung cysts. Patients should be counseled on pneumothorax symptoms, and a high baseline resolution CT of the chest should be performed with follow-up scans every 3 to 5 years. There is no data to support the idea that patients with BHDS should be advised against air travel. However, they should be counseled on smoking cessation to prevent pneumothoraces. Additionally, a full-body skin examination at routine intervals to evaluate for suspicious pigmented lesions should be implemented since there may be an association between malignant melanoma and BHDS.

Differential Diagnosis

Firm, dome-shaped papules present on the head and neck in several other syndromes. Multiple hamartoma syndromes (Cowden syndrome) presents with multiple trichilemmomas on the face, neck, and ears. It has an autosomal dominant inheritance and also is associated with oral papillomas, which create a cobblestone surface texture on the lips and mucosa. They also may have acral keratoses and cardiomegaly. Hornstein-Knickenberg syndrome (HKS) is in the differential diagnosis as well, which is also autosomal dominant and characterized by cutaneous, flesh-colored papules or perifollicular fibromas, but is further differentiated by a propensity for colonic neoplasms and polyps. Some experts also argue that perifollicular fibromas are the same lesions of BHDS but cut in different section planes and that HKS and BHDS are on the spectrum of disease.

Similarly, tuberous sclerosis and Brooke-Spiegler also can present with flesh-colored papules. Tuberous sclerosis, due to a defect in *TSC-1* or *TSC-2* gene, presents with angiofibroma, collagenomas, hypopigmented macules, and periungual fibromas. Angiofibromas also can occur in BHDS but are a less prominent feature. Additionally, they can have overlap features of fibrofolliculomas. Brooke-Spiegler syndrome results from a defect in the *CYLD* gene, and patients present with spiradenomas, trichoepitheliomas, and cylindromas. Trichoepitheliomas are firm, flesh-colored nodules that concentrate on the nasolabial folds, nose, upper lip, and scalp. Basaloid follicular hamartoma syndrome also presents with similar flesh-colored lesions; however, they gradually become pinker in color and plaque-like. Biopsy of the lesions and obtaining a thorough review of systems, past medical history, and family history often can provide clues to narrow the differential diagnosis of flesh-colored papules on the face.

Lung cysts and pneumothorax may also occur in lymphangioleiomyomatosis, emphysema, and pulmonary Langerhans cell histiocytosis. Renal tumors are features of von Hippel-Lindau syndrome and hereditary leiomyomatosis. Most pneumothoraces and renal carcinomas are sporadic.

Pearls and Other Issues

Genetic testing and counseling should be offered to near relatives older than the age of 20 years.

Enhancing Healthcare Team Outcomes

Birt-Hogg-Dube syndrome (BHDS) is an autosomal dominant genodermatosis, usually manifesting in the third decade of life with multiple fibrofolliculomas, trichodiscomas, and acrochordons. Because of the risk of malignancies later in life, these patients are best managed by an interprofessional team that includes a geneticist, pulmonologist, thoracic surgeon, dermatologist, nurse practitioners in dermatology, urologist, and primary care providers including internists, family physicians, and nurse practitioners. Specialty trained nurses in dermatology and genetics need to provide education to patients to avoid smoking and have regular imaging studies to detect cystic/solid lesions. Patients with this syndrome have an increased susceptibility to renal cell carcinoma, lung cysts, and spontaneous pneumothorax. Caution against air travel should be exercised.[10]

Review Questions

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