Birt-Hogg-Dubé syndrome: diagnosis and management

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Birt-Hogg-Dubé syndrome (BHD) is an autosomal dominant condition characterised clinically by skin fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax, and renal cancer. The condition is caused by germline mutations in the *FLCN* gene, which encodes folliculin; the function of this protein is largely unknown, although FLCN has been linked to the mTOR pathway. The availability of DNA-based diagnosis has allowed insight into the great variation in expression of *FLCN*, both within and between families. Patients can present with skin signs and also with pneumothorax or renal cancer. Preventive measures are aimed mainly at early diagnosis and treatment of renal cancer. This Review gives an overview of current diagnosis and management of BHD.

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Introduction

In 1977, Birt, Hogg, and Dubé described a pedigree in which several family members had skin lesions, consisting of "fibrofolliculomas with trichodiscomas and acrochordons".[1] Birt-Hogg-Dubé syndrome (BHD) is currently defined as an autosomal dominant condition, caused by germline mutations in the *FLCN* (folliculin) gene, and characterised by skin fibrofolliculomas (figure 1), multiple lung cysts, spontaneous pneumothorax, and renal cancer (Online Mendelian Inheritance in Man #135150).

In 2001, a BHD-associated gene locus was localised to chromosome 17p11.2 by linkage analysis.[2,3] Subsequently, truncating germline mutations were identified in a novel gene, the *FLCN* (*BHD*) gene, coding for a protein of unknown function called folliculin (FLCN).[4] At present, about 200 families with BHD with pathogenic *FLCN* mutations have been reported worldwide.[5–11] Roth and colleagues[12] first observed bilateral renal cancer in a 61-year-old patient with BHD, in 1993, and now an increased risk of renal cancer in carriers of *FLCN* mutations is firmly established.[13–16] Multiple lung cysts and spontaneous pneumothorax are also typical complications of the syndrome.[14,17]

BHD is probably under-diagnosed because of the wide variability in its clinical expression. Patients might present with renal cancer[18–20] or pneumothorax,[6,21–25] both of which most often occur sporadically. An estimated 25% of *FLCN*-mutation carriers older than 20 years of age do not manifest skin lesions,[5,7] whereas other mutation carriers have inconspicuous fibrofolliculomas.

FLCN is located on chromosome 17p11.2; the gene contains 14 exons and encodes folliculin, an evolutionary conserved protein of 579 aminoacids that has no major homology to any other human protein. The function of folliculin is largely unknown. Somatic second-hit mutations identified in BHD-associated renal tumours[26] are consistent with a tumour-suppressor function for FLCN. In line with these findings, loss of *FLCN* mRNA expression was found in renal tumours from patients with BHD.[27] However, *FLCN* mRNA was reported to be strongly expressed in fibrofolliculomas[27] and Van Steensel and colleagues[28] did not detect loss of heterozygosity in fibrofolliculomas, suggesting that mechanisms of tumorigenesis might differ in renal and skin tumours.

The Nihon rat model for BHD harbours a germline mutation of the rat *Flcn* orthologue.[29] In this animal model, renal cancer develops with high penetrance and with histological features that resemble human chromophobe renal cancer.[30] In heterozygous rats, introduction of wild-type *Flcn* resulted in suppression of renal carcinogenesis.[31] Fibromatous tumours associated with surgical incisions were observed; however, this phenomenon has not been reported in humans.[32]

Lingaas and co-workers[33] investigated an inherited cancer syndrome in German Shepherd dogs that showed multifocal renal cystadenocarcinoma and nodular dermatofibrosis. The researchers identified a missense mutation in the canine orthologue of the *FLCN* gene as the cause of this condition. Second-hit mutations were found in most of the renal tumours and in about a third of the early cystic renal lesions.[34,35] Loss of heterozygosity was not found in skin tumours, a result that is similar in humans.[28]

The energy-sensing mammalian target of rapamycin (mTOR) pathway has been implicated in the pathogenesis of several hereditary hamartoma syndromes, including BHD.[36,37] Baba and colleagues[38] identified a 130-kDa FLCN-interacting protein, FNIP1, and showed that it interacted with 5'AMP-activated protein kinase (AMPK), a protein involved in the mTOR pathway. An FNIP homologue, FNIP2, was found to interact with FLCN and AMPK.[39,40] Two studies described renal tumours and cysts

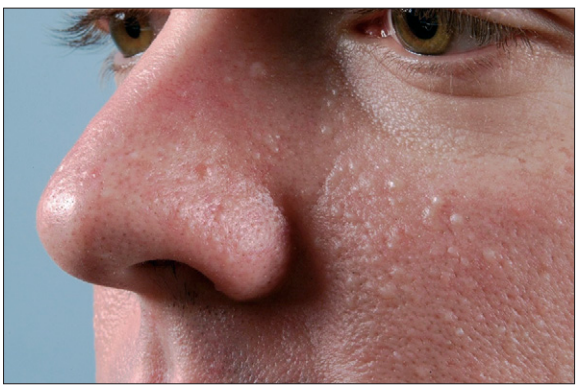

Figure 1: **Multiple, dome-shaped, whitish papules on the nose and cheeks in a 31-year-old carrier of an *FLCN* mutation**

and activation of mTOR in kidney-targeted BHD conditional knockout mice.[41,42] In this animal model, the mTOR-inhibitor rapamycin diminished kidney pathology and increased survival.

The tuberous-sclerosis-complex genes *TSC1* and *TSC2* encode proteins that regulate the mTOR pathway, and two studies[43,44] highlighted the overlapping clinical features of BHD and tuberous sclerosis complex (skin hamartomas, pulmonary cysts, pneumothorax, and renal tumours). However, yeast (*Schizosaccharomyces pombe*) that were missing the homologue of human *FLCN* had a phenotype opposite to yeast deficient for *TSC1* or *TSC2*.[43] Downregulation of FLCN leads to mTOR inhibition; by contrast, downregulation of TSC proteins leads to mTOR activation.[44] The precise role of folliculin in the mTOR pathway requires further elucidation, and it seems likely that folliculin has several functions. Clarifying the role or roles of folliculin in the molecular pathogenesis of renal cancer might lead to targeted therapy in selected patients.

A germline *FLCN* mutation was found by sequence analysis, in 51 of 61 families (84%) with BHD.[4,5] Most of the reported pathogenic *FLCN* mutations are frameshift or nonsense mutations that lead to protein truncation, and a small percentage are splice-site alterations. A mononucleotide tract of eight cytosines within exon 11 has been identified as a hypermutable hotspot;[4,45] the most frequently observed mutation is a cytosine insertion c.1285dupC.[5,7] Very few missense *FLCN* mutations were reported (eg, 1523A→G [Lys508Arg]).[7] Families without a detectable mutation might harbour a genomic deletion or amplification. Recently, an MLPA (Multiplex Ligation-dependent Probe Amplification) kit for *FLCN* deletion and amplification analysis has been developed. An *FLCN* mutation database has been established by Wei and colleagues[46] and by the European BHD Consortium.[47] So far, no gene other than *FLCN* has been implicated in BHD. In this Review, we summarise the diagnosis and management of BHD. Most of the recommendations are based on expert opinion and may serve as a basis for collaborative studies that could lead to evidence-based recommendations in the future.

For more on the **Multiplex Ligation-dependent Probe Amplification kit** see www.mlpa.com

For more on the ***FLCN* mutation databases by Wei and colleagues** see www.skingenedatabase.com

For more on the ***FLCN* mutation database by the European BHD Consortium** see www.lovd.nl/flcn

For more on **BHD collaborative research** see www.europeanbhdconsortium.eu

For more on **BHD and renal tumours** see www.cancer.gov/cancertopics/types/kidney

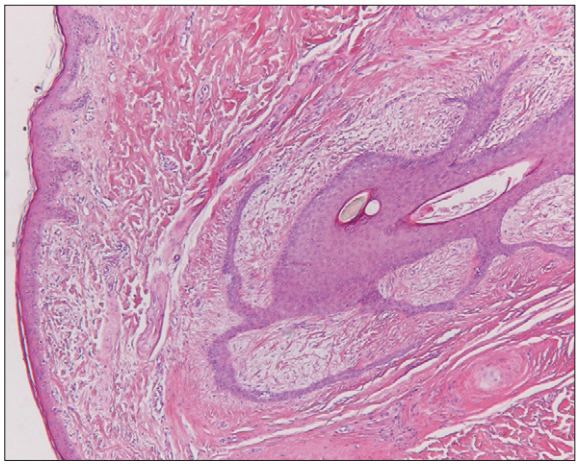

Figure 2: **A fibrofolliculoma consisting of interanastomosing septa of follicular epithelium in and around a perifollicular fibrous proliferation with centrally a dilated hair follicle**
Courtesy of L Rozendaal.

Clinical manifestations

The skin

Skin lesions in patients with BHD usually appear after the age of 20 years, as multiple, dome-shaped, whitish papules in the face. These lesions are mainly on the nose and cheeks (figure 1), can be common on the neck, and are sometimes on the trunk or the ears. Histologically, the skin tumours are benign hair follicle tumours designated as fibrofolliculoma (figure 2).

Birt and colleagues[1] described fibrofolliculomas, trichodiscomas, and acrochordons as a triad of skin lesions that characterise BHD. Currently, fibrofolliculomas and trichodiscomas are considered to be part of a morphological spectrum. Acrochordons, or skin tags, are common in the general population. In BHD, skin tags might represent a phenotypic variant of fibrofolliculoma.[48–50] BHD-associated skin lesions might also include angiofibroma.[51] Multiple facial angiofibromas are more typically associated with tuberous sclerosis than with BHD, which should be considered in the differential diagnosis of BHD. Oral lesions may also occur in BHD. Toro and co-workers[13] found multiple, discrete soft papules involving the lips, buccal mucosa, and gingiva in nine patients with BHD, underscoring the case report by Nadershahi and colleagues.[52]

The diagnosis of BHD-associated skin lesions is based on both clinical presentation and histological examination. Multiple biopsies and sectioning of the lesions on several levels might be required for correct classification. Expert advice might be necessary when the diagnosis is in doubt. Starink and colleagues[53] described familial multiple trichodiscomas as a separate syndrome from BHD, emphasising the early onset of skin lesions. So far, childhood onset of fibrofolliculomas has not been reported in carriers of *FLCN* mutations. Therefore, families with trichodiscoma or fibrofolliculoma but without pulmonary or renal manifestations of BHD and without a pathogenic *FLCN* defect might represent a distinct syndrome.

The kidneys

The most threatening complication of BHD is renal cancer. In a series by Pavlovich and colleagues,[15,16] 34 of 124 individuals (27%) with BHD had renal tumours at a mean age of 50·4 years (range 31–74 years). Other studies reported a history of renal cancer at age 27 and metastatic clear-cell renal cancer at the same age.[20,54] The earliest reported age at diagnosis of renal cancer in a patient with BHD is 20 years.[45]

Zbar and colleagues[14] found a seven-times increase in the risk of renal cancer for BHD-affected individuals.

However, the risk of renal cancer in BHD is uncertain for several reasons. First, identification of families with BHD has varied and was mostly based on dermatological signs. Second, the risk of renal cancer might not be the same for all BHD families. In particular, families with pathogenic *FLCN* mutations have been described in whom lung cysts and pneumothorax were the only or predominant clinical manifestations.[6,21–25] In theory, interfamilial variations in cancer risk might be due to different classes of *FLCN* mutations; however, so far no convincing genotype–phenotype correlations have been shown. Based on current data, the risk of renal cancer should probably be considered the same for all carriers of *FLCN* mutations, for patients with BHD, and for at-risk relatives without identified *FLCN*-mutations.

Chromophobe renal cancer (figure 3) and a mixed pattern of chromophobe and oncocytic renal tumours are typical for patients with BHD. However, other histological subtypes can occur, including clear-cell and papillary carcinoma, and several mixed patterns.[15,16,19,20,55] Pathogenic *FLCN* mutations were found in 4·3% of cases of familial clear-cell renal cancer without evidence of renal-cancer susceptibility syndromes.[11] Renal cancer is multifocal or bilateral in more than half of patients with BHD,[15,16] which has implications for clinical management.

Relatively few patients with BHD and metastatic renal cancer have been described in literature. Prospective studies with a large number of patients are needed to clarify the biological behaviour of BHD-associated renal cancer.[7] Benign renal cysts have been documented in patients with BHD,[13,20] but the exact frequency of these cysts in comparison with the prevalence in the general population is currently unknown.

The lungs

On CT examination of the thorax, more than 80% of adult patients with BHD had multiple lung cysts. By contrast with sporadic primary pneumothorax, where pulmonary cysts are typically found in the apical zones, the lung cysts in BHD are most often located in the basal lung regions (figure 4).[7,17,56,57] The histology of pleuropulmonary lesions in BHD has been studied in several patients and is consistent with emphysematous changes.[6,58,59]

The lung parenchyma generally appears normal in patients with BHD, and despite the presence of multiple lung cysts, lung function is usually unaffected.[17] Zbar and colleagues[14] found a 50-times increase in the risk of pneumothorax for BHD-affected individuals; this increase is probably related to the presence of lung cysts.[17] In one series of patients with BHD, the prevalence of pneumothorax was 24%, with a median age at first occurrence of 38 years (range 22–71).[17] Pneumothorax has been reported in *FLCN*-mutation carriers at the age of 7 years and 16 years.[60,61] Patients may have a single episode of spontaneous pneumothorax, but recurrent disease is more common.[17]

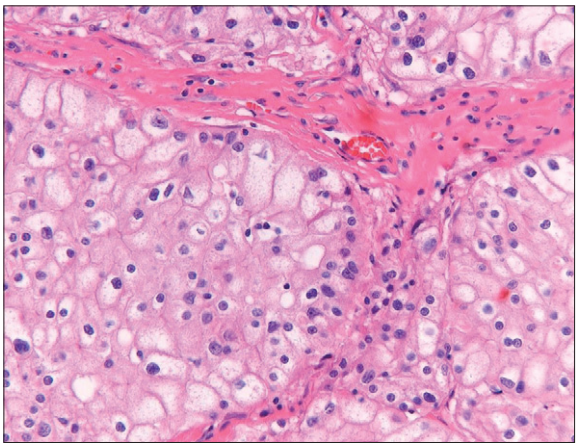

Figure 3: **Chromophobe renal cancer (haematoxylin-eosin staining, magnification x20) in a 51-year-old carrier of an *FLCN* mutation**
Courtesy of L Rozendaal.

Although there is no clear indication for routine CT scanning of the lungs in patients with BHD, the demonstration of multiple lung cysts strengthens the diagnosis when it is in doubt.

Underlying *FLCN* mutations have been detected in several families with apparently non-syndromic cystic lung disease or pneumothorax.[6,9,21,61–63] Smoking is an important risk factor for spontaneous primary pneumothorax; however, the role of smoking as a risk factor in BHD has been not been fully clarified.[17,59] No association was found between *FLCN* alterations and chronic obstructive lung disease.[64]

Other clinical findings

Co-occurrence of BHD and a range of tumours other than renal cancer has been reported. Benign tumours include multinodular goiter, parotid-gland adenoma and oncocytoma, colorectal polyp and adenoma, neural-tissue tumour, trichoblastoma, connective-tissue nevus, focal-cutaneous mucinosis, lipoma, angiolipoma, and cutaneous leiomyoma.[5,7,10,65–75] Malignant tumours include breast cancer, colorectal cancer, sarcoma of the leg, tonsillar cancer, lung cancer, melanoma, basal and squamous-cell skin cancer, dermatofibrosarcoma protuberans, and cutaneous leiomyosarcoma.[7,10,12,43,71,72,74] So far, a causal relationship between BHD and these benign and malignant tumours has not been proven.

In 1975, Hornstein and Knickenberg described the combination of skin fibrofolliculomas and colorectal polyps.[65] Hornstein–Knickenberg syndrome is now considered to be identical to BHD, but whether BHD is associated with an increased risk of colorectal adenoma and cancer is uncertain. Colonoscopy assessment in 45 patients with BHD did not show an increased prevalence of colorectal neoplasms.[14] However, as proposed by Khoo and co-workers,[45] an increased risk of colorectal cancer might apply only to specific subgroups of patients. In addition to benign and malignant

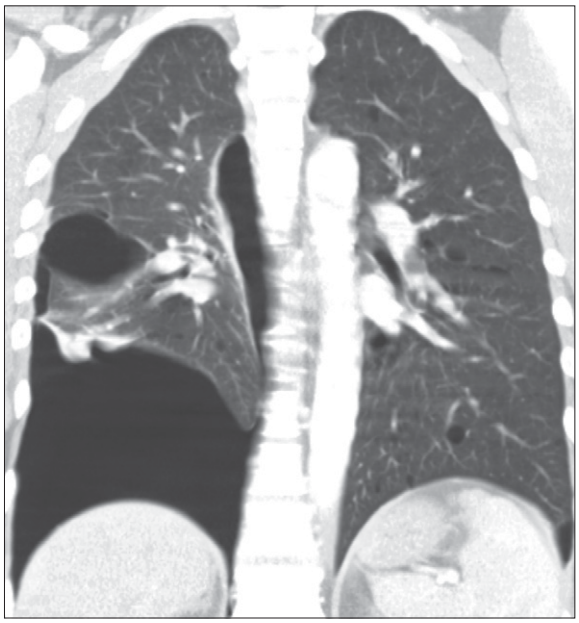

Figure 4: **CT scan of the thorax of a 26-year-old carrier of an *FLCN*-mutation who had multiple episodes of pneumothorax bilaterally; right-sided pneumothorax and bilateral lung cysts**
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tumours, various other abnormalities were observed in patients with BHD, including chorioretinopathy,[73,76] internal carotid-artery aplasia,[77] congenital cystic lung soft-tissue mass,[63] and congenital chest deformation.[20] It is unclear whether any of these abnormalities are causally related to BHD.

Criteria for diagnosis

DNA-based diagnosis of hereditary tumour syndromes has led to new classifications of these conditions based on the underlying gene defects. BHD was formerly defined by the presence of at least five to 10 fibrofolliculomas, of which at least one papule was diagnosed histologically.[13,45] However, the identification of *FLCN* defects in families with BHD has led to new insights in the penetrance and clinical variability of this syndrome. For example, *FLCN*-mutation carriers might not manifest any skin lesions. We propose diagnostic criteria that are based on clinical manifestations and the outcome of DNA testing (panel). All patients suspected of having BHD should be offered genetic testing to confirm the diagnosis.

Multifocal or bilateral renal cancer (or both) with hybrid chromophobe and oncocytic histology is a hallmark of BHD, but unifocal and unilateral clear-cell cancer can also occur. Therefore, BHD should be considered in patients who do not fulfill the diagnostic criteria but still might have an underlying *FLCN* mutation. These are patients with early-onset renal cancer (<50 years), in particular with multifocal or bilateral disease (or both) with chromophobe or oncocytic histology. Patients might have unexplained cystic lung disease, pneumothorax, or both, especially if the lung cysts are bilateral and basally located. Additionally, patients should be considered who have familial cystic lung disease, pneumothorax, familial renal cancer, or any combination of spontaneous pneumothorax and kidney cancer in an individual or family. For these patients, referral for a clinical assessment, pedigree analysis, and *FLCN* mutation analysis should be considered.

In families with cystic lung disease or pneumothorax only, or renal cancer only, a definite diagnosis of BHD can only be made if a pathogenic *FLCN* germline mutation is detected.

BHD should be differentiated from other syndromes with similar signs and symptoms. In particular, tuberous sclerosis complex should be considered; patients with this syndrome might show facial angiofibroma, lung cysts and pneumothorax due to lymphangioleiomyomatosis, and renal cysts and tumours.[50,78]

Our proposed diagnostic criteria for BHD and indications for *FLCN* mutation analysis should be assessed in prospective studies.

Genetic testing

FLCN is currently the only gene known to be associated with BHD. DNA-based diagnosis should ideally consist of sequence analysis and a test for exonic deletions and amplifications. Genetic testing should always involve genetic counselling. Mutation detection is recommended even when the clinical diagnosis of BHD is unambiguous: detection of a pathogenic *FLCN* mutation not only confirms the diagnosis in the index patient but also allows presymptomatic testing of unaffected at-risk relatives. This testing is especially important because of the clinical variability of the syndrome: adult at-risk relatives without skin fibrofolliculomas can carry the familial mutation.

When a pathogenic mutation has been detected, cascade genetic testing aimed at identifying and counselling at-risk family members is indicated. Surveillance in *FLCN*-mutation carriers usually begins at the age of 20 years. In most centres, presymptomatic diagnosis is postponed until the age of 16–18 years to allow counselling and informed consent before genetic testing. However, earlier testing and surveillance might be indicated in rare circumstances, for example in families with very early onset of pneumothorax or renal cancer.

Management

The skin

Treatment for skin fibrofolliculomas should be discussed, since the psychological burden of having numerous facial fibrofolliculomas should not be underestimated. However, current therapeutic options are limited. Case reports indicate that laser ablation using an erbium:YAG or fractional CO_2 laser is not curative, but gives temporary

improvement.[79–81] Al-Daraji and colleagues[82] reported successful shave and cautery treatment. Farrant and Emerson[83] advocated curettage and hyfrecation of lesions as an alternative for laser treatment. Pendulous fibrofolliculomas, or skin tags, can often be easily excised. Malignant skin tumours have occurred in BHD, but they do not develop from fibrofolliculomas; these malignant tumours might be coincidental and not part of the syndrome.

The kidneys

Because of the increased risk of renal cancer, surveillance for renal tumours is indicated for carriers of *FLCN* germline mutations, and for patients and at-risk relatives in families with clinical BHD but without confirmed *FLCN* mutation. Currently, there are no established guidelines regarding surveillance for renal cancer in BHD—ie, the optimum age to start surveillance, the method or methods of examination, and the interval between procedures. The reported age range of renal cancer in BHD is mainly between 25–75 years, so the best age to start surveillance might be 20 years. The main methods for surveillance are CT, MRI, and renal ultrasonography. Choyke and colleagues[84] reviewed surveillance in hereditary renal cancer and discussed CT and MRI as options; they considered ultrasonography to be too insensitive for small renal masses. Detection rates of 100% for CT and 58% for ultrasonography were reported for lesions 15–20 mm, 100% and 79% for lesions 20–25 mm, and 100% and 100% for lesions 25–30 mm.[85] Apparently, ultrasonography had a low sensitivity for small lesions. Lifetime screening is needed for individuals with BHD or those at risk for the syndrome, and repeated CT-scanning would give an unacceptably high cumulative radiation dose.[86,87]

Annual renal MRI seems to be the best available surveillance method, with high sensitivity and no radiation side-effects; however, MRI might not be readily available in all centres. Annual ultrasonography is offered in many centres, although the precise sensitivity of this method in detecting renal tumours in BHD disease is currently unknown. BHD renal-cancer screening programmes should be carefully reviewed and audited to ensure detection rates are adequate.

If renal cancer is diagnosed, staging is done with standard procedures.[88] Treatment consists of nephron-sparing surgery (open or laparoscopic partial nephrectomy), if technically feasible, to be done by an expert urological surgeon. As in other hereditary syndromes with multifocal and bilateral renal cancer, treatment aims to spare renal function and prevent metastatic disease. In hereditary renal cancer, particularly Von Hippel–Lindau disease, a lesion size of 3 cm is usually recommended as the threshold for parenchyme sparing surgery,[89–91] but there is limited experience with this policy in BHD.[16,90] Other factors to consider are the growth rate and location of the tumour(s). Minimally invasive nephron-sparing techniques such as cryoablation and radiofrequency ablation[92] might be considered for tumours smaller than 3 cm. Since in-vitro and animal studies suggest that loss of *FLCN* results in deregulation of the mTOR pathway, rapamycin analogues could be considered as possible candidates for therapy in patients with disseminated renal cancer.

Panel: **Diagnostic criteria for Birt-Hogg-Dubé syndrome (BHD; patients should fulfill one major or two minor criteria for diagnosis)**

Major criteria

- At least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset*
- Pathogenic *FLCN* germline mutation

Minor criteria

- Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax
- Renal cancer: early onset (<50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology
- A first-degree relative with BHD

*Fibrofolliculoma and trichodiscoma are two possible presentations of the same lesion—for the differential diagnosis, angiofibroma in tuberous sclerosis should be considered. Childhood-onset familial fibrofolliculoma or trichodiscoma without other syndromic features might be a distinct entity.

The lungs

Exposure to large ambient pressure differences could precipitate pneumothorax in patients with BHD. Individuals for whom specific risks apply, particularly piloting and deep-sea diving, should be referred to a pulmonary physician for diagnosis and advice. Currently, there is no evidence that patients with BHD should be advised against air travel. However, patients with a history of recurrent pneumothorax or with signs or symptoms of pulmonary disease should be assessed by a pulmonary physician. Assessment of lung involvement by thoracic CT scan should be considered before surgery that requires general anaesthesia.

Treatment is similar for sporadic primary pneumothorax and pneumothorax in patients with BHD. Referral to an expert centre might be indicated if there is a history of recurrent pneumothorax or specific indications (eg, regular flying). Smoking is an important risk factor for both spontaneous pneumothorax and renal cancer. Although there are limited data on smoking and the risk of pneumothorax and renal cancer in BHD,[17,59] smoking might increase the risk of these disease manifestations and should be strongly discouraged in this group of patients.

Conclusion

BHD syndrome was first characterised on the basis of skin fibrofolliculomas—one of the major features. Multiple fibrofolliculomas, histologically verified, are probably diagnostic for the syndrome, although a distinct syndrome with fibrofolliculomas or trichodiscomas only has not been excluded. For the differential diagnosis, tuberous sclerosis

Search strategy and selection criteria

References for this Review were found through a search of Pubmed by use of the terms "Birt-Hogg-Dubé syndrome", "fibrofolliculoma", or "FLCN". Reference lists of relevant articles were reviewed. Only full-text articles were included. No date or language restricitons were used. Selected references on associated topics were also included.

For more on **patient support groups for BHD** see www.bhdsyndrome.org

complex is an important consideration, since fibrofolliculomas in BHD and angiofibromas in tuberous sclerosis complex have overlapping features. With the identification of causative *FLCN* germline mutations, it is now evident that clinical expression of BHD varies greatly. Patients can have unrecognised, inconspicuous fibrofolliculomas or even no skin manifestations at all. The syndrome can also be identified by the other main clinical features: spontaneous pneumothorax and renal cancer. Particularly in patients with pneumothorax, skin signs or BHD features in family members can lead to diagnosis, as well as multiple lung cysts, which occur in most adults with BHD. BHD-associated renal cancer shares general features with other types of hereditary renal tumours: early age at diagnosis and multifocal or bilateral disease. Additionally, a seemingly unique feature of BHD renal tumours is the mix of histological subtypes; a hybrid pattern of chromophobe cancer and oncocytoma is typical. This pattern in patients with renal cancer, along with other features of BHD in the patient or close relatives, can lead to the diagnosis. In families with a characteristic pattern of clinical features, *FLCN* mutation analysis leads to a confirmed diagnosis in most cases. Identification of the causative mutation offers the possibility of predictive testing in family members.

Preventive measures are largely aimed at early recognition and treatment of renal cancer. The optimum programme for surveillance has not yet been established. A yearly MRI scan of the kidney starting at age 20 years is probably best, but the exact role of CT and ultrasonography has not been fully investigated. Therefore, surveillance should ideally be organised in the framework of a study programme. Advice to stop smoking is the only available strategy to possibly prevent pneumothorax. Precautions can also be taken for circumstances which might precipitate pneumothorax, such as general anaesthesia.

Because colorectal cancer can occur in a subgroup of families with BHD, periodic colonoscopy might be considered in such families with cases of colorectal cancer or advanced colorectal adenomas. More information is needed on the risks of colorectal adenomas and cancer in BHD. Surveillance for other tumours that have been occasionally reported in families with BHD is not generally recommended.

The identification of the *FLCN* gene has allowed the further investigation of clinical variability and molecular mechanisms of BHD. Several groups collaborate on clinical and fundamental research on the syndrome. Collection of family data in registers dedicated to monitoring of patients will provide information on clinical variability and outcome measures that will allow clinicians to adjust diagnostic criteria and management recommendations. From a molecular point of view, insight in the cellular pathways involved in pathogenesis of BHD might lead to specific options for early diagnosis and targeted therapies. *FLCN* mutation databases have been established. Patient support groups are important sources for information on issues of particular importance for patients and family members. Because of the preliminary nature of much of the data on BHD, current recommendations should be reassessed as further information becomes available.

Contributors

FHM drafted the article. FHM, MAMvS, and ERM wrote the final manuscript. All authors participated in critical revision and final approval of the article.

Conflicts of interest

The authors declared no conflicts of interest.

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