VU VRIJE UNIVERSITEIT AMSTERDAM

VU Research Portal

Renal and Pulmonary Aspects of Birt-Hogg-Dubé syndrome

Johannesma, P.C.

2016

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)
Johannesma, P. C. (2016). *Renal and Pulmonary Aspects of Birt-Hogg-Dubé syndrome*.

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:
vuresearchportal.ub@vu.nl

Download date: 27. Jan. 2022

Chapter 4.2.

Nederlandse Samenvatting (voor leken)

Paul C. Johannesma[1]

[1] Afdeling Longziekten, VU Medisch centrum, Amsterdam, Nederland

Voor de introductie van diagnoses middels DNA onderzoek, wat sinds 1990 mogelijk mogelijk is sinds 1990, werden erfelijke tumor (kanker) syndromen alleen herkend middels een verzameling van uiterlijke karakteristieken. Deze karakteristieken bevatten kenmerken die bij de patiënt gezien werden, waarbij er tevens een familiaire belasting van deze aandoening was.
Sinds 1990 zijn in toenemende mate erfelijke tumor syndromen op DNA niveau geïdentificeerd. Op basis hiervan kunnen tegenwoordig (gezonde) patiënten – waarbij de familie belast is met een tumor syndroom - gescreend worden op DNA niveau om het erfelijke syndroom te bevestigen.
Een voordeel van het testen middels DNA, is dat bij patiënten met minimale uiterlijke kenmerken het syndroom al bevestigd kan worden.
Doordat er veel onderzoek gedaan wordt op het niveau van DNA naar tumorsyndromen, ontdekt men ook meer verbanden tussen syndromen en kunnen er gerichtere therapieën worden ontwikkeld voor het behandelen van de klinische verschijnselen van deze syndromen.

Een goed voorbeeld van een syndroom dat in eerste instantie werd gediagnosticeerd middels uiterlijke kenmerken, maar vele jaren later werd bevestigd op DNA niveau, is het zogenoemde Birt-Hogg-Dubé syndroom. In 1977 beschreven de huidarts dokter Birt, de patholoog dokter Hogg en de internist dokter Dubé een grote familie met uiterlijke kenmerken van een syndroom. De familieleden hadden allen karakteristieke huidafwijkingen die de drie dokters “fibrofolliculomen”, “trichodiscomen” en “acrochordons” noemden. De stamboom liet een autosomale dominante overerving zien (dus geen voorkeur voor geslacht, 50% kans op overerving door volgende generatie) met uiterlijke kenmerken vanaf de leeftijd van 25 jaar. Later ontdekte men dat het syndroom tevens gepaard ging met een verhoogde kans op het ontwikkelen van nierkanker en (terugkerende) spontane klaplong (pneumothorax). In 2002 werd het syndroom ontdekt op DNA niveau bij een afwijking op de korte arm van het 17^{e} chromosoom. Doordat het syndroom nu bevestigd kon worden op DNA niveau, kon een screeningsprogramma van de nieren opgestart worden en was het mogelijk nierkanker in een vroeg stadium ontdekt en behandeld worden.

Hoewel de huidafwijking “fibrofolliculoom” zeer specifiek is voor het Birt-Hogg-Dubé syndroom, is het heel lastig om de klaplong en nierkanker bij dit syndroom te onderscheiden van de klaplong en nierkanker bij patiënten zonder dit syndroom. Hoewel voorkomen van nierkanker op jonge leeftijd,

voorkomen van nierkanker bij andere familieleden en aanwezigheid van kanker in beide nieren kenmerkend is voor een erfelijke vorm, is dit lastig te onderscheiden van nier-erfelijke nierkanker. Ook klaplong als uiting van een syndroom is lastig te onderscheiden van niet-erfelijke klaplong, aangezien de lichamelijke klachten in beide gevallen hetzelfde zijn. Daarnaast komen de huidafwijkingen, nierkanker en klaplong niet bij alle patiënten met dit syndroom voor, daarom is het soms lastig om een patroon te vinden en het syndroom te onderkennen. De focus in dit proefschrift ligt op de longen en de nieren. Door de uiterlijke kenmerken, lichamelijke klachten en familiaire patronen van deze patiëntengroep onder loep te leggen, hopen we in de toekomst het syndroom sneller te kennen, wat zal leiden tot een snellere en betere optimale behandeling. De belangrijkste bevindingen van dit proefschrift worden hieronder beschreven:

Deel 1: Pulmonale (long) karakteristien binnen het Birt-Hogg-Dubé syndroom.

Tot op heden is het nog steeds onduidelijk hoe cysten (holten) onderin de longen bij patiënten met het Birt-Hogg-Dubé syndroom (BHD) zich ontwikkelen. In **hoofdstuk 1.1** hebben we een follow-up (in tijd opvolgende) studie gedaan onder 6 patiënten met het BHD syndroom. Hierin toonden we aan dat hoewel cysteuze longaandoeningen normaalgesproken progressief (verergerend) van aard zijn, dit niet het geval is bij patiënten met BHD. We veronderstelden (hypothese) dat de holten in mindere mate zich kunnen oprekken, waardoor deze barsten. Doordat de holten barsten kan de lucht uit de long stromen en ontwikkelt de patiënt een klaplong. We evalueerden de CT-scan van 6 patiënten, waarbij we de scan na 44 maanden herhaalden en vonden geen groei in grootte, aantal, locatie of vorm van de cysten (holten). We legden deze bevinding naast de bevinding dat oudere patiënten met het BHD syndroom niet vaker een klaplong ontwikkelden, en concludeerden op basis van deze gegeven dat BHD op het gebied van de longen geen progressieve aandoening is. Dat patiënten met het syndroom een klaplong ontwikkelen is dus waarschijnlijk meer het gevolg van drukverschil waardoor de holten knappen.[1 2]

In **hoofdstuk 1.2.** stellen we de hypothese dat een CT-scan van de longen een belangrijke rol van betekenis kan spelen in het opstellen van de juiste behandeling van klaplong en het geven van de juiste leefstijl adviezen. Daarom evalueerden we in dit hoofdstuk alle BHD patiënten met een beschikbare CT-scan en vergeleken we de groep mét en de groep zonder doorgemaakte klaplong in

het verleden. We includeerden hiervoor 61 met BHD. De grootste studie tot nu toe wereldwijd. Het enige verschil in de twee groepen bleek het aantal cysten in de longen te zijn, waarbij er geen relatie met leeftijd was. Derhalve concludeerden we dat er mogelijk een relatie tussen het aantal cysten en de kans op het ontwikkelen van een klaplong kan zijn.[3]

Based on the fact that over 90% of BHD patients have clinically detectable cysts in basal parts of the lung, we hypothesized in **chapter 1.3**. that use of a low dose chest CT might be an effective way to detect this syndrome in patients presenting with apparently isolated PSP. Early diagnosis of BHD is important for the patient and his or her family members. inheritance is autosomal dominant, and the condition is associated with a lifetime risk of renal cell cancer of approximately15%. In this study we included 46 pneumothorax patients, 19 of which had proven BHD based on a *FLCN* germline mutation and 27 were negative in *FLCN* mutation analysis, thereby excluding BHD as good as possible. We found a higher prevalence of recurrent SP among patients with a proven pathogenic *FLCN* mutation, a higher incidence of episodes of pneumothorax and a higher number of cysts. On thoracic CT the distribution, location and size of the cysts differed significantly from those in patients without BHD syndrome. We found that in BHD cases the majority of cysts had a size < 2cm and this probably explains why these abnormalities cannot be detected using standard erect chest X-ray. It is likely that in addition to air trapping other mechanisms play a role in the development of a pneumothorax. In the apical parts of the lung the pleural stress is high and abnormalities in that area are likely to increase the risk of rupture.[4] In BHD-patients the majority of cysts are located close to the pleura in the lower lobes, which makes it likely that the wall of cysts connected to the visceral pleura ruptures easily.[5] Important for this is the lack of stretching possibilities of the wall of lung cysts of BHD patients.[6] As such this study is the largest study so far in literature, the main limitation remains the small number of patients we included. As this syndrome is relatively rare, it is difficult to gather a large cohort of patients. Although there seems to be a clear distinction on thoracic CT between BHD patients and patients without BHD, the rarity of this syndrome may still lead to unawareness among doctors who have to evaluate these thoracic CT's. Despite lacking information in this study on all clinical information regarding smoking history, familial inheritance on pneumothorax and prior (surgical) treatment of pneumothorax , we suggested that the radiological distinction between BHD and patients without BHD can easily be made on a low dose CT scan of the thorax.

The first episode of PSP usually occurs in the third decade in males, who are often taller than age-matched controls, and the majority has a history of smoking. Smoking increases the risk of PSP more than 100 times.[7] PSP diagnosis is usually based on history and confirmed by a standard erect chest X-ray during inspiration. Although we showed in **chapter 1.2.** and **chapter 1.3.** a significant difference in thoracic imaging among BHD patients and patients without BHD who had a history of SP, it is radiologically still difficult to distinguish between BHD and smoking as a cause for SP. This difficulty is discussed in **chapter 1.4**. Therefore we describe a possible role for TTF-1 staining of the inner cyst wall, which might be specific for BHD.

In **chapter 1.5.** we assessed the relationship between air travel or diving and the occurrence of spontaneous pneumothorax in a large cohort of BHD patients with a proven pathogenic *FLCN* mutation. A questionnaire was sent to a cohort of 190 patients and the medical files of these patients were evaluated. In total 158 (83.2%) patients returned the completed questionnaire. Sixty-one of 145 patients who had ever travelled by airplane had a history of SP (42.1%), with a mean of 2.48 episodes (range 1-10), 24 (35.8%) had a history of bilateral episodes. Thirteen patients developed SP <1 month after air travel and 2 patients developed a SP <1 month after diving. Symptoms possibly related to undiagnosed SP were perceived in 30 patients (20.7%) after air travel, respectively in 10 patients (18.5%) after diving. Based on the results reported in this chapter, we suggest that exposure of BHD patients to considerable changes in atmospheric pressure leads to an increased risk of developing a symptomatic pneumothorax. Symptoms reported during or shortly after flying and diving might be related to the early phase of pneumothorax.

The literature regarding the risk for SP after diving in patients with lung cysts is extremely limited. The British Thoracic Society (BTS) guideline recommends that diving is permanently avoided after an episode of spontaneous pneumothorax unless the patient has undergone bilateral surgical pleurectomy and lung function and postoperative thoracic CT are normal.[8] [9] [10] Our results are comparable to the study results of the interstitial lung disease lymphangioleiomyomatosis with an incidence of 1.1 pneumothoraces per 100 patients.[11] [12]

Based on the study of Ren et al, which showed in 9.8% of cases a pathogenic *FLCN* mutation, among 102 patients with apparently primary SP (PSP), we evaluated in **chapter 1.6.** the prevalence of BHD among patients with apparently primary spontaneous pneumothorax (PSP).[13] Among the 40 patients with apparently common PSP, three had pathogenic germline *FLCN* mutations and one of these had a positive family history for pneumothorax. All three patients had multiple basal lung cysts. Asymptomatic renal cell cancer was detected in a first- degree family member of an identified BHD patient. The main limitations of this study were the low response rate and a possible selection of cases.

The response rate was low, since only 40 out of a total group of 316 patients (9.9%) were fully examined. Patients who were invited for the study may preferentially have opted for this possibility due to certain characteristics for example young age at diagnosis, high recurrence rate or a positive family history for the disease. In addition, the letter in which the study was explained contained information on characteristics of BHD patients i.e. skin lesions or a personal or family history of pneumothorax of renal cancer and this may have encouraged selected individuals to participate. However, as the results of the group of 40 patients is in line with the much larger study by Ren[13] and colleagues in consecutive cases with PSP, selection bias may not have been a major factor in this study.

The recurrence rate of SP in BHD has been described in literature to be as high as 75%, therefore we retrospectively evaluated the effect of different types of treatment in **chapter 1.7.** Current BTS and ACCP guidelines do not describe the treatment of SP in BHD patients as a separate entity. In this study we compared the results of treatment in a comparable group of BHD and non-BHD patients with (recurrent) SP. We found a recurrence rate of 64.5% after conservative treatment and a recurrence rate of 11.1% after invasive treatment of SP in BHD patients. This recurrence rate was significantly higher when compared to recurrence risk in patients without BHD. Therefore invasive treatment might be the better option for BHD patients with (recurrent) SP. Our results suggest that SP in BHD is associated with a high recurrence rate after conservative treatment and an invasive therapy would therefore be the best approach in this group.

<u>Part two: Renal manifestations.</u>

In **chapter 2.1.** the clinical data of 115 *FLCN* mutation carriers from 35 BHD families are evaluated. Among 14 *FLCN* mutation carriers who developed renal cancer 7 were <50 years at onset and/or had multifocal/bilateral tumours. Five symptomatic patients developed metastatic disease. Two early-stage cases were diagnosed by surveillance. The majority of tumours showed characteristics of both eosinophilic variants of clear cell and chromophobe carcinoma. The estimated penetrance for renal cancer and pneumothorax was 16% (95% minimal confidence interval: 6-26%) and 29% (95% minimal confidence interval: 9-49%) at 70 years of age, respectively. The most frequent diagnosis in families without identified *FLCN* mutations was the rare syndrome of familial multiple discoid fibromas identified in a large Dutch family. Based on these results we confirm the importance of surveillance for renal cancer in BHD patients. As renal tumours in BHD patients do not evidently differ from sporadic tumours in growth or histological pattern, it remains difficult to clinically distinguish between BHD-associated and sporadic renal cancer.

The prevalence of BHD among patients with apparently sporadic RCC is unknown. The histological subtype and clinical presentation of RCC in BHD are highly variable. In **chapter 2.2.** we showed the results of our retrospective study among patients diagnosed with sporadic RCC, wherein we retrospectively scored for the presence of lung cysts on thoracic CT. We performed *FLCN* mutation analysis in 8 RCC patients with at least one lung cysts under the carina. No *FLCN* mutations were identified. We compared the radiological findings in the *FLCN* negative patients to those in four BHD patients and found multiple basal lung cysts were present significantly more frequent in *FLCN* mutation carriers. We therefore advise that in all RCC patients at least a concise family history is taken for the presence of RCC or SP and that the skin is examined for the presence of fibrofolliculomas. In the presence of a positive family history (SP or RCC) or multiple basal lung cysts further investigation of BHD is indicated (e.g. by dermatological evaluation or by DNA testing). The difficulty in unmasking BHD patients in apparently sporadic RCC patients is illustrated in this study by the negative family history for pneumothorax and RCC in the two *FLCN* mutation carriers.
Notably, skin lesions can also be early signs of hereditary predisposition for RCC in other syndromes, in particular hereditary leiomyomatosis and renal cell cancer.

In current literature renal surveillance in BHD is recommended, but the optimal imaging method and screening interval remain to be defined. In **chapter 2.3.** we retrospectively evaluated the compliance to, and the outcomes of renal cancer surveillance in patients diagnosed with BHD in two centers. Screening data of 199 patients diagnosed with BHD in two hospitals were collected. All available renal imaging follow up data and the medical records of 23 BHD patients with renal cell carcinoma (RCC) were collected. Initial screening was performed in 171/199 patients (86%) and follow up data were available from 117/171 patients (68%). The total follow-up period was 499 patient years. Of the patients that performed follow-up screening, 85% was screened at least yearly and 96% at least every two years. A medical history of RCC was present in 23 patients, 38 tumours were diagnosed with a mean age of the diagnosis of the first tumour at 51 years. In 21 tumours ultrasound (US) was performed. Eleven tumours, sized 7-27 mm, were visible on MR or CT and not detected using US. This study indicated that compliance to renal screening is relatively high and that US might be a sensitive, cheap and widely available imaging modality for detecting clinically relevant renal tumours in BHD patients, since no tumours exceeding 3 cm were missed with US.

Part three: Relevant case reports and case series

In chapter 3.1. we evaluated a patient with BHD that developed pneumothorax following flying and was manifested later. We consider the pressure changes during the subsequent flights as potential trigger for initiating rupture of a subpleural cyst, this implies that the interval between air travel and the diagnosis is important. In other studies 50% of cysts were located in the subpleural area and less than 5% abut on bronchioles. So if a cyst would be connected to the bronchial tree, the size of connection to the airways is very small, resulting in small volumes of air transported into the pleural cavity. Therefore it will probably take a long time before troublesome symptoms are present. Also spontaneous resolution of a small pneumothorax after rupture of a subpleural cyst may occur if there is no active transport of gas into the pleural cavity. Based on this theory we concluded that BHD patients who have minimal chest symptoms after the first flight should be checked for pneumothorax before the return flight.

Although clinical manifestation usually appears after the age of 20, we discussed in **chapter 3.2.** two cases of BHD wherein episodes of (recurrent) pneumothorax occurred from the age of 14. Lung cysts were seen in both patients, mainly in the basal parts of the lung. SP has been reported only twice in pediatric pathogenic *FLCN*-mutation carriers. [14] [15] As SP in the pediatric population is relatively rare, BHD should be considered as underlying cause, especially when there is a positive family history for pneumothorax. Easy accessible genetic testing for BHD in pediatric patients with (recurrent) spontaneous pneumothorax should be performed, even when skin manifestation is absent. Based on this case series, more research on the prevalence of BHD in the pediatric population with a history of (recurrent) spontaneous pneumothorax might be needed.

In **chapter 3.3** we describe the case of a former Olympic swimmer who was referred to our hospital due to recurrent episodes of pneumothorax. Although the patient never smoked and the patient had multiple recurrences of SP, BHD was not suggested in this patient. This case shows the difficulty of recognizing this syndrome and the difficulty to distinguish this syndrome from common PSP.

An illustrative kindred is presented in **chapter 3.4.** in which the index patient had recurrent episodes of pneumothorax without apparent skin lesions or renal abnormalities. He had bilateral basally located lung cysts. Family members had fibrofolliculomas, lung cysts, pneumothorax and clear cell renal cancer. The described family highlights the importance for doctors to ask for family history regarding pneumothorax and renal cancer.

In **chapter 3.5.** we evaluated a patient who presented with skin fibrofolliculomas. Based on the diagnosis of multiple fibrofolliculomas BHD was suspected and an abdominal CT was performed. The abdominal CT showed a solid intrapolar tumour in the lower pole of the right kidney. We concluded in this chapter that BHD should be considered when facial fibrofolliculomas are diagnosed and consequently relatives should be stimulated to undergo genetic testing.

A patient with apparently sporadic chromophobe renal cell cancer is discussed in **chapter 3.6.** As the patient had a positive history for spontaneous pneumothorax and renal cancer, BHD was suspected, which was confirmed after molecular testing. We evaluated in this chapter the importance of

recognizing this autosomal dominant cancer disorder when a patient is presented at the urologist with a positive family history of chromophobe renal cell cancer, or a positive familial history for renal cell cancer and pneumothorax.

Finally, in **chapter 3.7** we describe a patient who was referred to the clinical geneticist due to fibrofolliculomas. Although thoracic CT showed no lung cysts, the patient had a history of recurrent episodes of pneumothorax. As BHD was suspected, an additional abdominal MRI was performed which showed an asymptomatic tumour in the left kidney. A pathogenic *FLCN* germline mutation was found in this patient, which was not found in both parents. This is the first publication that describes a de *novo FLCN* mutation. *De novo FLCN* mutations are probably rare, but might be under-diagnosed. We suggest that BHD should be considered in patients who present with one or more of the syndromic features despite a negative family history.

References

[1] Toro JR, Pautler SE, Stewart L, et al. Lung cysts, spontaneous pneumothorax, and genetic associations in 89 families with Birt-Hogg-Dubé syndrome. Am. J. Resp. Crit. Care Med. 2007; 175:1044-1053.

[2] Clarke BE. Cystic lung disease. J. Clin. Pathol. 2013;66: 904-908.

[3] Onuki T, Goto Y, Kuramochi M, et al. Radiologically indeterminate pulmonary cysts in Birt-Hogg-Dubé syndrome. Ann Thorac Surg. 2014;97:682-685.

[4] Casha AR, Manché A, Gatt R, et al. Is there a biomechanical cause for spontaneous pneumothorax? Eur J Cardiothorac Surg. 2014;45:1011-1016.

[5] Johannesma PC, Houweling AC, van Waesberghe JHTM, et al. The pathogenesis of pneumothorax in Birt-Hogg-Dubé syndrome: a hypothesis. Respirology 2014; 19: 1248-1250.

[6] Medvetz DA, Khabibullin D, Hariharan V, et al. Folliculin, the product of the Birt-Hogg-Dubé tumor suppressor gene, interacts with the adherens junction protein p0071 to regulate cell-cell adhesion. PLoS ONE 2012;7: e47842.

[7] Smit HJ, Chatrou M, Postmus PE. The impact of spontaneous pneumothorax, and its treatment, on the smoking behavior of young adult smokers. Respir Med. 1998;92:1132-1136.

[8] MacDuff A, Arnold A, Harvey J; BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. Thorax 2010; 65 Suppl 2:ii18-31.

[9] Hoshika Y, Kataoka H, Kurihara M, et al. Features of pneumothorax and risk of air travel in Birt-Hogg-Dubé syndrome. *Am J Respir Crit Care Med* 2012; 185:A4438.

[10] Baumann MH. Pneumothorax and air travel: lessons learned from a bag of chips. Chest 2009; 136:655-656.

[11] Taveira-DaSilva AM, Burstein D, Hathaway OM, et al. Pneumothorax after air travel in lymphangioleiomyomatosis, idiopathic pulmonary fibrosis, and sarcoidosis. Chest 2009; 136:665-670.

[12] Pollock-BarZiv S, Cohen MM, Downey GP, et al. Air travel in women with lymphangioleiomyomatosis. Thorax 2007; 62:1756-1780.

[13] Ren HZ, Zhu CC, Yang C, et al. Mutation analysis of the *FLCN* gene in Chinese patients with sporadic and familial isolated primary spontaneous pneumothorax. Clin Genet 2008; 74:178-183.

[14] Bessis D, Giraud, Richard S, et al. A novel familial germline mutation in the initiator codon of the BHD gene in a patient with Birt-Hogg-Dubé syndrome. Br J Dermatol. 2006;155:1067-1069.

[15] Gunji Y, Akiyoshi T, Sato T, et al. Mutations in the Birt-Hogg-Dubé gene in patients with multiple lung cysts and recurrent pneumothorax. J Med Genet 2007;44:588-593.