Early detection of hereditary renal cell cancer by improved evaluation of spontaneous pneumothorax patients

Paul C. Johannesma, MD

E-mail: p.johannesma@vumc.nl

VU University Medical Center
Department of Pulmonary Diseases
Amsterdam, The Netherlands
Disclosures

I have no financial or other conflicts of interest to report
Pneumothorax

“An abnormal collection of air or gas in the pleural space between the visceral and parietal pleura”

**TABLE 1. CLASSIFICATION OF PNEUMOTHORAX ACCORDING TO CAUSE.**

- **Spontaneous**
  - Primary: no clinical lung disease
  - Secondary: a complication of clinically apparent lung disease

- **Traumatic**
  - Due to penetrating chest injury
  - Due to blunt chest injury

- **Iatrogenic**
  - Due to transthoracic-needle aspiration
  - During placement of a catheter in the subclavian vein
  - Due to thoracentesis and pleural biopsy
  - Due to barotrauma

Spontaneous Pneumothorax diagnosed on chest X-ray
Imaging Chest X-ray versus Thoracic CT
Familial predisposition for pneumothorax

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene(s)</th>
<th>Chromosomal location</th>
<th>Frequency Spontaneous Pneumothorax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan syndrome</td>
<td>Fibrillin 1</td>
<td>15q21.1</td>
<td>4.4-11%</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Cystathionine β-synthase</td>
<td>21q22.3</td>
<td>“minor feature”</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>Multiple</td>
<td>Multiple</td>
<td>“rare reports”</td>
</tr>
<tr>
<td>α1-Antitrypsin deficiency</td>
<td>α1-Antitrypsin deficiency</td>
<td>14q32.1</td>
<td>“rare reports”</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td>TSC2</td>
<td>16p13</td>
<td>55%</td>
</tr>
<tr>
<td>Birt-Hogg-Dubé syndrome</td>
<td>Folliculin</td>
<td>17p11.2</td>
<td>30%</td>
</tr>
</tbody>
</table>
Clinical Presentation of Birt-Hogg-Dubé syndrome (BHD)

- Skin (Fibrofolliculomas)
- Lung cysts and (recurrent) spontaneous pneumothorax
- Renal cell cancer
- No geno- phenotype correlation found thus far
Pulmonary characteristics

- Lung cysts basal parts of the lung >90% of BHD patients
- Lung function unaffected
- 50-times increase in the risk of pneumothorax
- Houweling et al: Estimated pneumothorax risk: 29% age 70 (95% CI: 9-49%%)
- Median age 38
- Reports of SP in pediatric patients with BHD

Renal cell cancer risk in BHD patients

Houweling et al, 2011: Lifetime risk 16% (95% CI: 6-26%)

Toro et al, 2007: 34% at initial screening


How frequent is BHD among patients with a primary SP?

Characteristics of three spontaneous pneumothorax patients with pathogenic \textit{FLCN} mutations

<table>
<thead>
<tr>
<th>Patient (fam no.)</th>
<th>Gender (Age first PSP)</th>
<th>Delay between first symptom (PSP) and final diagnosis \textit{BHD} (in months)</th>
<th>Recurrence of PSP</th>
<th>No. of recurrences PSP</th>
<th>Number of lung cysts</th>
<th>Renal tumour</th>
<th>FF</th>
<th>Smoking history</th>
<th>\textit{FLCN} mutation</th>
<th>Counselled first degree family members</th>
<th>Found RCC in counselled family members</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (84)</td>
<td>F (20)</td>
<td>243</td>
<td>Yes</td>
<td>8</td>
<td>13</td>
<td>No</td>
<td>Minimal</td>
<td>no</td>
<td>c.610_611delGCinsTA (p.Ala240X)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2 (85)</td>
<td>M (26)</td>
<td>153</td>
<td>Yes</td>
<td>6</td>
<td>140</td>
<td>No</td>
<td>Minimal</td>
<td>no</td>
<td>c.1408_1418del (p.Gly470fs)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3 (94)</td>
<td>M (40)</td>
<td>81</td>
<td>Yes</td>
<td>3</td>
<td>74</td>
<td>No</td>
<td>No</td>
<td>no</td>
<td>c.1539-2A&gt;G</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Comparable to study of Ren et al. (2008): 9.8\% pathogenic \textit{FLCN} mutation carriers among 102 primary SP patients


“This leads us to the question; If a thoracic CT would be performed in all SP patients and the patients with cysts in lower parts of lungs would be tested for BHD, how many RCC could then be detected?”

Cohort BHD patients; VU University Medical Center

- Retrospective evaluation
- 2004-2014
- 55 families
- N=200
- Mean 3.6 patients/ family (1-20)
Evaluation of clinical and radiological characteristics among 200 *FLCN* mutation carriers in BHD 55 families.

So far detection of BHD associated with SP revealed 15 RCC patients in our cohort with mean FU of 5 years (1-10)
Current advice if BHD is detected

1. **FLCN** mutation analysis of at-risk family members
2. Surveillance of mutation carriers with renal imaging

2. Two new cases of RCC found during follow up (mean: 5 years follow up)
3. Extrapolating (2/115)x100 = 1.74 new cases per 5 years follow up
4. 0.30 new cases / 100 cases / year
5. 3 new cases of RCC /1000 cases/ year
Theoretical extrapolation current data:

1. Screening for pathogenic \( FLCN \) mutation of 3.6 patients per BHD family

2. Diagnosing 100 (new) families > 360 pathogenic \( FLCN \) mutation carriers

3. At age 70; 6-26\%* lifetime risk to develop RCC will lead to 33-94 new RCC patients

* 95\% Confidence Interval


Flowchart for spontaneous pneumothorax

- RCC in medical history?
  - Familial SP
  - Familial RCC

FlCN mutation analysis

Thoracic CT:
- Basal Lung cysts?

+ Family counseling
+ Renal MRI
+ Dermatological consultation
Conclusion

• In our pilot study 7.5% of all SP caused by pathogenic *FLCN* mutation

• Including (low dose) thoracic CT can lead to identification BHD families

• Annual renal imaging offered to affected relatives > detection RCC

• Limited period of observation leads to detection of RCC at early stage
Acknowledgements

M.A. Jonker, PhD
J.J.P. Gille, PhD
A.C. Houweling, MD PhD
Q Waisfisz, PhD
E. Thunnissen, MD PhD
R. Reinhard, MD
J.H.T.M. van Waesberghe, MD PhD
M.A. Paul, MD PhD
Prof. Th.M. Starink, MD PhD
Prof R.J.A. van Moorselaar, MD PhD
Prof P.E. Postmus, MD PhD

F.H. Menko, MD PhD
Prof. S. Horenblas, MD PhD
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