Familial pneumothorax

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Take home messages: Several genetic disorders can present as spontaneous pneumothorax. A definitive diagnosis can have important beneficial long-term consequences by enabling precision care of potentially life-threatening complications.

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Introduction

The leakage of air into the pleural space in the absence of trauma or gross lung pathology is called primary spontaneous pneumothorax (1). This condition has been recognised for more than two centuries and has been treated by thoracocentesis (needle aspiration) for almost as long (2). Primary spontaneous pneumothorax is a disorder predominantly of younger people and, with an incidence of 12.5 per 100,000 per year (3), is not especially rare. It is estimated that 1 in 200 tall, thin, young men (the asthenic phenotype) might develop a pneumothorax at some stage. Although primary spontaneous pneumothorax carries very little risk of death, recurrent pneumothoraces, which happen in 30-50% of cases, can cause distress both due to pain and through interference with normal activities such as sport and travel (2). Primary pneumothoraces are believed to occur because of the rupture of small bullae or blebs at the surface of the lung (4). Owing to the effect of gravity, the apical portions of human lungs are subject to the most stretch. In tall individuals, especially those who smoke, this can cause enlargement of airspaces and the development of emphysematous changes that result to bleb formation. Here, we will discuss an approach to the investigation and management of pneumothorax with a focus on identification of underlying genetic causes.

Clinical Management

Because of a deficit of good evidence, the British Thoracic Society (BTS) and American College of Chest Physicians (ACCP) based their pneumothorax guidance largely on non-analytical studies and expert opinion (5-7). To address this, several groups are currently trying to determine the most effective therapies. Some of these studies are expected to report over the next two to three years. At present, initial treatment is determined by the size of the presenting pneumothorax. A "small" pneumothorax is treated conservatively so long as there is no respiratory compromise, while a "large" pneumothorax is treated first by aspiration, followed by intercostal chest drain if necessary. Surprisingly, there is little consensus as to what represents a large pneumothorax: the ACCP use a >3cm pleural separation at the apex, whereas the BTS use 2cm at the hilum; however, direct comparison between these two definitions showed poor correlation (8). Recently, we compared the BTS and ACCP definitions and observed that, if followed correctly, the BTS guidance would lead to the insertion of fewer unnecessary chest drains, while the ACCP guidance would encourage drain insertion in some patients who would do well even with conservative management (7). The flip side of this, however, is that patients treated conservatively according to the BTS guidance do, on occasion, re-present early requiring further intervention. Better biomarkers are therefore required

to predict the need for chest drain insertion. In addition, ambulatory management of pneumothorax has become an option to reduce the need for hospital admission (2). For many years, the Heimlich flutter valve has been available for treatment of pneumothoraces, but physicians have been reluctant to discharge patients home with large drain *in situ* (9). Small self-contained pleural drainage devices are now available and their effectiveness is being determined, e.g. by the RAMPP study (ISRCTN79151659 DOI 10.1186/ISRCTN79151659).

Familial pneumothorax

Remarkably, 1 in 10 patients who present with a spontaneous pneumothorax report having a first or second degree relative who had also suffered a pneumothorax (10). This points towards a large heritable component in this condition, yet in the majority of cases a genetic diagnosis is not made. We argue that efforts should be made to define the genetic cause in cases of familial pneumothorax because, although the pneumothorax itself carries little risk of mortality, it may be the harbinger of a life-shortening genetic disorder. By making a genetic diagnosis early, it is possible to anticipate serious manifestations of a genetic disease before they occur and, by pre-emptive treatment, avoid life-threatening complications. A table of potential disorders and their underlying genetics is presented (Table 1).

Birt-Hogg Dubé syndrome

Pneumothorax can lead to the diagnosis of Birt-Hogg Dubé syndrome [OMIM #135150], which accounts for roughly 15% of familial cases (11). This autosomal dominant disease is characterised by medial-basal lung cysts (Figure 1), several types of benign skin growths (fibrofolliculomas, trichodiscomas, angiofibromas, perifollicular fibromas) and renal malignancies (clear cell and renal cell carcinoma, papillary renal cell carcinoma, renal oncocytoma and chromophobe renal carcinoma). Some families exhibit a *forme fruste* of the condition characterised predominantly of lung cysts and pneumothoraces without clear evidence of skin involvement. It is not yet clear whether they also have a higher risk of renal cancer

Birt-Hogg-Dubé syndrome is caused by mutations of the *FLCN* gene, encoding folliculin (11). It is important to identify *FLCN* mutations because of the increased risk of renal cancers they impart, 16-27% over a lifetime (11,12). Ninety per cent of patients with *FLCN* mutations will have lung cysts on CT scan and their risk of developing pneumothorax is high (13). It has been estimated that 29% of patients with Birt-Hogg-Dubé syndrome will develop a pneumothorax (14). Because the mean age of first pneumothorax is much earlier than that of renal malignancies, it offers an opportunity to make an early diagnosis and so alter the long-term survival of patients and their

affected relatives (11). Renal cell carcinomas are very often cured if excised whilst still small and so tumours are usually excised surgically before they reach 3cm. Lifelong renal follow-up either by annual renal MRI or ultrasound scan is therefore recommended in patients with proven Birt-Hogg-Dubé syndrome (13).

Marfan syndrome

Although the asthenic build of many patients presenting with pneumothorax often makes clinicians think of Marfan syndrome [#154700] this is more rarely seen in the pneumothorax clinic than Birt-Hogg-Dubé syndrome. Nevertheless, it is an important diagnosis to make because of its cardiovascular associations, in particular ascending aortic dissection. Death can be delayed or avoided in these patients by careful management of blood pressure combined with regular echocardiography to monitor for evidence of worsening aortic root dilatation. Prophylactic aortic root replacement can be lifesaving when the aortic root reaches 4.5-5 cm (15).

Marfan syndrome is an autosomal dominant condition caused by mutations of the *FBN1* gene, encoding fibrillin-1 (16). Unfortunately, unlike mutations of *FLCN*, genetic testing is hampered because *FBN1* is highly polymorphic, meaning that sequencing will frequently identify novel variants of uncertain clinical significance. Careful clinical phenotyping is therefore important so that a diagnosis can be made using the revised Ghent criteria (Table 2) (17).

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome is a group of six connective tissue disorders that are subdivided based on their clinical, biochemical and genetic features of which hypermobility and thin, translucent skin are the most common (18,19). Type IV, also known as vascular Ehlers-Danlos syndrome, can be associated with pneumothoraces (20). These patients can have an autosomal dominant mutation in the *COL3A1* gene resulting in abnormal collagen deposition, leading to fragility of the pleura and the formation of subpleural blebs (21). The importance of an early diagnosis relates to the susceptibility of these patients to spontaneous rupture of the bowel and arteries.

Loeys-Dietz syndrome

Recently, a further autosomal dominant connective tissue disorder called Loeys-Dietz syndrome was identified (10,22). This is characterised by vascular abnormalities (cerebral, thoracic and abdominal arterial aneurysms and dissections) and skeletal features (pectus excavatum or carinatum, scoliosis, joint laxity, arachnodactyly, and talipes equinovarus) caused by mutations in components of the transforming growth factor (TGF)-β signalling pathway (10,22). Interestingly, mice with defects in the TGF-β pathway show abnormal midline fusion (23), and humans similarly

can show cleft palates or, more subtly, have a bifid uvula (Figure 2). We recently reported that Loeys-Dietz syndrome can present with pneumothorax prior to clinical manifestation of its vascular complications (10). As with Marfan syndrome, this allows subsequent monitoring by echocardiography and, if needed, early surgical intervention to treat aneurysms. Medical management with angiotensin receptor blockade appears also to be helpful in slowing the development of aneurysms.

Lymphangioleiomyomatosis

Overall, pneumothorax is less common in women, with a male:female ratio of 3:1. A rare but important cause of pneumothorax in women is lymphangioleiomyomatosis (LAM), a multisystem disorder affecting women of childbearing age (Figure 3). Although LAM is not itself heritable, it is strongly associated with the autosomal dominant disorder tuberous sclerosis caused by mutations of *TSC1* [OMIM #191100] or *TSC2* [#613254]. The main pulmonary feature of LAM is multiple cysts scattered throughout the lungs (24) (Figure 3). Extrapulmonary features include angiomyolipomas and lymphatic tumours such as lymphangioleiomyomas, which can cause chylous pleural effusions through blockage of the thoracic duct. Pneumothoraces tend to be recurrent and are seen in about 50-60% of patients with LAM (24). If the lung is biopsied, the cysts are seen to be surrounded by abnormal smooth muscle cells that stain positively for HMB-45, but frequently the diagnosis can be made without tissue sample with a characteristic CT scan in combination with extrapulmonary features. Recently, raised blood levels of VEGF-D were noted in LAM and are increasingly being used as a diagnostic test by specialist centres (25).

Importantly, LAM can be a progressive disease of reducing lung function for which, until recently, the only treatment was lung transplantation. However, because of its association with mutations of *TSC1* and *TSC2*, a link between LAM and the mTOR signalling pathway was made (24). This led to the discovery that rapamycin, an inhibitor of mTOR, can slow the rate of decline of lung function in LAM (26).

Rarer genetic causes

Rarer genetic causes include autosomal recessive conditions such as homocystinuria and cutis laxa. Homocystinuria [#236200] is a disorder of sulfur metabolism that leads to an accumulation of homocysteine in the body. It shares many features of Marfan syndrome, including increased risk of pneumothoraces, but it is distinguished by also causing intellectual disability and downward dislocation of lens (17,27). Cutis laxa [#219200] is characterised by loose skin, especially over the face and trunk (28). Because its association with emphysematous change in the lung, it too can present with pneumothoraces.

Conclusion

Primary pneumothorax clearly has a strong heritable component with 10% of cases showing an autosomal dominant pattern of inheritance. Several of the underlying conditions have life-threatening long-term complications that can be ameliorated if an early diagnosis is made. Careful phenotyping of pneumothorax patients is therefore essential, but even in a dedicated pulmonary genetics services providing such precision medicine, roughly 60% of cases remain unclassified. For this reason, familial pneumothorax has recently been included by Genomics England as one of the disorders being addressed by the 100,000 Genomes Project. For more information see https://www.genomicsengland.co.uk/the-100000-genomes-project/.

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Condition	Affected genes	Clinical features
Birt-Hogg-Dubé syndrome	*FLCN*	1) Lung cysts 2) Benign skin growths 3) Renal malignancies
Marfan syndrome	*FBN1*	See Ghent criteria, Table 2
Ehlers-Danlos syndrome	*COL5A1, COL5A2, TNXB, COL3A1, PLOD1, COL1A1, COL1A2, ADAMTS2*	1) Hypermobility 2) Thin, translucent skin 3) More features depending on subtype
Loeys-Dietz syndrome	*TGFBR1*, *TGFBR2*, *TGFB2*, *SMAD3* (TGF-β pathway)	1) Vascular abnormalities (aneurysms, dissections) 2) Skeletal features (e.g. pectus excavatum)
Lymphangioleiomyomatosis	*TSC1*, *TSC2* (through link to tuberous sclerosis)	1) Multiple lung cysts 2) Angiomyolipomas 3) Lymphangioleiomyomas
Homocystinuria	*CBS* (most common), *MTHFR, MTR, MTRR, MMADHC*	1) Similar to Marfan syndrome 2) Learning disability 3) Downward lens dislocation
Cutis laxa	*ATP6V0A2, ATP7A, EFEMP2, ELN, FBLN5*	1) Loose skin, especially over face and trunk 2) Emphysema

Table 1. Disorders associated with pneumothorax and their underlying genetics

Marfan syndrome

(1) Aortic diameter at the sinuses of Valsalva (Z score ≥2) AND ectopia lentis

(2) Aortic diameter at the sinuses of Valsalva (Z score ≥2) AND known disease-associate *FBN1* mutation

(3) Aortic diameter at the sinuses of Valsalva (Z score ≥2) AND systemic score* (≥7pts)

(4) Ectopia lentis AND aortic disease-associate *FBN1* mutation

(5) Ectopia lentis AND Family history of Marfan syndrome

(6) Systemic score (≥7 pts) AND Family history of Marfan syndrome

(7) Aortic diameter at the sinuses of Valsalva (Z≥2 above 20 years old, ≥3 below 20 years) AND Family history of Marfan syndrome

***Scoring of systemic features:**

- Wrist AND thumb sign – 3 (wrist OR thumb sign – 1)
- Pectus carinatum deformity – 2 (pectus excavatum or chest asymmetry – 1)
- Hindfoot deformity – 2 (plain pes planus – 1)
- Pneumothorax – 2
- Dural ectasia – 2
- Protrusio acetabuli – 2
- Reduced upper segment/lower segment ratio AND increased arm/height AND no severe scoliosis – 1
- Scoliosis or thoracolumbar kyphosis – 1
- Reduced elbow extension – 1
- Facial features (3/5) – 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
- Skin striae – 1
- Myopia > 3 diopters - 1
- Mitral valve prolapse (all types) – 1

Maximum total: 20 points; score ≥7 indicates systemic involvement

Table 2. Revised Ghent criteria for the diagnosis of Marfan syndrome. Adapted from (17).

Legends

Figure 1. Birt-Hogg Dubé syndrome.

Coronal reformatted thoracic computed tomograph (CT) (lung windows setting) of a patient with Birt-Hogg-Dubé syndrome. Note the basal and medial preponderance of irregular cysts, some of which are multiseptated. This patient previously had a left-sided pleurectomy and at the time of the CT had a tiny loculated left pneumothorax. Consent.

Figure 2. Loeys-Dietz syndrome.

(A) Chest radiograph demonstrating left apical pneumothorax.

(B) Photograph of patient's uvula.

(C) Coronal reformat of chest computed tomography (CT) (lung windows setting). Arrowheads: numerous small subpleural blebs at both apices.

(D) Sagittal reformat of contrast-enhanced CT of thoracic aorta. Black lines shows maximal dimensions of the aortic root at the sinus of Valsalva (3.54 cm), confirmed by echocardiography, and sinotubular junction (2.93 cm). Reproduced from (10).

Figure 3. Lymphangioleiomyomatosis (LAM).

Thoracic computed tomograph (CT) (lung windows setting) of a patient with LAM. Note the thin-walled cysts scattered throughout the lungs separated by apparently normal lung parenchyma. This patient had previously undergone bilateral pleurectomies, but at the time of this scan had bilateral loculated pneumothoraces, which were subsequently treated by CT-guided chest drain insertion. Consent.