Phenotyping primary spontaneous pneumothorax

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In the era of personalised medicine, there is a need to "phenotype" primary spontaneous pneumothorax in order to tailor the most appropriate treatment for each patient http://ow.ly/slNX30lizXz

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Spontaneous pneumothorax is one of the most common disorders affecting the pleura. A large epidemiological study in France from 2008 to 2011 reported an estimated annual rate of non-traumatic pneumothoraces of 22.7 cases per 100 000 inhabitants, with a male to female ratio of 3.3 to 1 [1]. 85% of the nearly 60 000 hospital admission episodes corresponded to primary spontaneous pneumothoraces (PSP) [1], a categorisation which implies that the person does not have a known lung disease. Despite spontaneous pneumothorax being frequent and first recognised as a distinct entity two centuries ago [2], only about 20 randomised controlled trials have been published to date, the vast majority of which comprised a small number of patients. Consequently, gaps still remain in the fundamental pathophysiological mechanisms and preferred management options. For instance, the assumption that the underlying lung is normal in PSP is debatable. PSP predominantly (~90%) occurs in tobacco smokers [3]. Airway inflammation is produced by tobacco and cannabis smoking and, thus, both contribute to the development of subclinical lung disease, particularly upper lobe bullous emphysema [3]. The general consensus is that rupture of subpleural blebs or bullae (usually located in the lung apices) into the pleural space plays a major role in PSP development. Most patients with a PSP who are thought to be free of parenchymal disease are found to have blebs, bullae (termed emphysema-like pulmonary changes) or apical opacities (*i.e.* linear opacities, focal subpleural consolidations or pleural thickening) on high-resolution computed tomography (HRCT) [4–6]. Abnormal regions of the visceral pleura detected by fluorescein-enhanced autofluorescence thoracoscopy, so-called "pleural porosity", have also been put forward as a potential cause to explain the occurrence of PSP [7]. However, pleural porosity, which hypothetically implies slow air leakage through the visceral pleura, is difficult to reconcile with the sudden start of PSP symptoms. According to the previous text, the distinction between PSP and secondary spontaneous pneumothorax is viewed increasingly as artificial. In the same line, the need to routinely obtain an HRCT to detect an underlying occult disease for clinical decision-making purposes during a first episode of a PSP should be considered, though not currently explicitly recommended by scientific guidelines [7–9]. In fact, HRCT imaging in patients presenting with an apparent PSP may be cost-effective even if only for the uncovering of infrequent diffuse cystic lung diseases, such as lymphangioleiomyomatosis, Birt–Hogg–Dubé syndrome or Langerhans cell histiocytosis [10]. Spontaneous pneumothorax occurs in around 60% [11], 75% [12] and 15% [13] of these entities, respectively, albeit with a very high likelihood of recurrence [14].

Other critical questions, with so far elusive answers, that may help optimise PSP management are the true risk of recurrences after a first episode and the identification of patients at this particular risk who could benefit from early preventive measures. The study by Walker *et al.* [15] in this issue of the *European*

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Respiratory Journal gives insight into these questions. They performed a meta-analysis of 29 studies (of which only four were randomised controlled trials) comprising more than 13 500 adult patients with a first episode of PSP who underwent medical management (*i.e.* observation, needle aspiration or chest drain). The overall recurrence rate (either ipsilateral or contralateral) was 32%, and at the 1 year mark it was 29%. Patient follow-up varied dramatically among studies (3 to 144 months). In another recently published systematic review that included 40 studies and 3904 patients with a first episode of PSP, the mean recurrence rate was found to be slightly less (22%) and the mean time to first recurrence was 20 months, but subjects who underwent surgical interventions were also included [16].

A relevant finding of the Walker *et al.* [15] study was that recurrence rates were significantly higher in women than men [15]. A possible reason might be the presence of some female-specific disease, such as catamenial pneumothorax (CP). A retrospective Japanese database identified 27 716 women who needed hospitalisation for spontaneous pneumothorax during a 6-year period [17]. Underlying lung diseases were reported in one-third of the cases, CP representing the fourth leading cause (873 cases), after interstitial pneumonia, lung tumours and chronic obstructive airway diseases. In another retrospective series, CP accounted for 21% of 51 females younger than 50 years of age with spontaneous pneumothoraces who were surgically treated [18]. Even after pleurodesis through video-assisted thoracoscopic surgery (VATS), 30–40% of CP patients experience recurrences during the following 2 years [18, 19]. In addition to the influence of the female gender in PSP recurrences, the other consistent conclusion of the Walker *et al.* [15] meta-analysis is the recognition that smoking cessation may be the most important strategy in preventing PSP, having been found to be associated with a 4-fold decrease in the risk of recurrence. Other potential predictors of recurrence such as a low body mass index or the presence of blebs or bullae on chest imaging were less consistently demonstrated, probably due to the significant heterogeneity of the included studies [15].

According to the current meta-analysis, patients with a new diagnosis of PSP should be informed that about one-third will have a recurrent episode, mostly during the next year, and this risk will be greatly increased in females. Nonetheless, the life-long recurrence risk may be higher. Paradoxically, existing guidelines do not recommend preventive procedures until the patient experiences a second ipsilateral PSP event [7, 8]. Should preventive therapies be reserved for recurrent PSP or should they be applied following the first episode, particularly in high-risk patients such as females? In a network meta-analysis of 10 randomised controlled trials, VATS ranked the highest in preventing recurrences in patients with a first episode of PSP, followed by pleurodesis [20]. In a second study, 181 patients with a first episode of PSP were randomised to receive VATS (plus bullectomy of visible blebs/bullae and mechanical pleurodesis) or conventional chest tube drainage [21]. At the 1-year follow-up, the recurrence rate in the chest tube group was significantly higher at 34% *versus* the 13% recurrence rate in the VATS group. Obviously, the benefits of any surgical procedure for such a low-risk mortality disease like PSP should outweigh the non-benefits. In a large prospective series of 1415 patients with recurrent PSP who were subjected to VATS with talc poudrage and, if necessary, bullectomy, complications occurred in 29 (2%) patients, of whom 24 (1.7%) had prolonged air leaks [22]. There was no mortality and further recurrences were identified in only 26 (1.9%) patients. Moreover, needlescopic [23] and uniportal [24] VATS are alternative effective options with potentially less postoperative pain and faster recovery that should be further explored in the future. Even if a preventive intervention is not advised *a priori* according to prevailing guidelines, should patients experiencing their first PSP episode and being treated with a chest tube for the initial management also undergo chemical pleurodesis to prevent future events?

In the era of personalised medicine, there is a need to "phenotype" PSP (*i.e.* to define categories according to the pathophysiology, clinical course or patient's occupation) in order to tailor the most appropriate treatment for each patient. Future guidelines should propose, despite the limited existing evidence, the use of diverse therapies for different clinical scenarios. Awareness of an unrecognised lung disease and/or categorisation of patients into a high-recurrence risk group may warrant more aggressive management at the initial PSP presentation. Large prospective randomised controlled trials and cost-effectiveness studies are urgently required to implement the most appropriate management strategies in PSP [25].

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