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Cough in interstitial lung disease

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ABSTRACT

Cough in the context of interstitial lung disease (ILD) has not been the focus of many studies. However, chronic cough has a major impact on quality of life in a significant proportion of patients with ILD. For the purpose of this review, we have chosen to highlight some of the more frequently encountered diffuse lung diseases including idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis and systemic sclerosis associated ILD. Many of the underlying mechanisms remain speculative and further research is now required to elucidate the complex pathways involved in the pathogenesis of chronic cough in ILD. This will hopefully pave the way for the identification of new therapeutic agents to alleviate this distressing and often intractable symptom.

Up to one third of the general population have experienced a chronic cough, defined as a cough persisting for more than 8 weeks. Most commonly, cough is post-infective or attributable to conditions such as upper airways cough syndrome (rhinosinusitis), gastro-oesophageal reflux, eosinophilic airways disease, and chronic obstructive airways disease (COPD) [1]. Many causes for cough are self-limiting or manageable, but more than four hundred million pounds are spent on over-the-counter medications per annum. The persisting cough afflicting many patients with interstitial lung disease (ILD), however, is characteristically intractable, and exerts a major impact on physical, psychological, and social wellbeing [2].

1. Cough reflex

Cough is a protective mechanism clearing the airways of noxious substances and accumulated secretions to preserve gas exchange, and is defined by three phases: inspiration, forced expiration against a closed glottis, and finally opening of the glottis [3]. It is triggered by both mechanical and chemical stimuli. The cough reflex arc comprises the following; 1) an afferent vagal sensory limb usually originating from the upper and lower airways (particularly the larynx and tracheo-bronchial tree); 2) convergence of signals in the nucleus tractus solitarius and processing in the central respiratory generator of the medulla oblongata; and 3) efferent motor limbs in the vagus (glottis closure), phrenic and spinal nerves supplying the laryngo-thoraco-abdomino-pelvic muscles [4,5]. Higher cortical centres can modify the cough response [6]. Several afferent nerve pathways have been identified in sub-serving this role and can be broadly classified into: -

- Mechanically-evoked pathways (tracheal touch-sensitive A-delta fibres or *cough receptors* and rapidly and slowly adapting airway mechanosensors) and
- Chemically-evoked pathways (bronchopulmonary unmyelinated C-fibres and chemosensitive A-delta fibres).

The reader is directed to several excellent reviews on this topic [7–10]. Activation of *cough receptors* and bronchopulmonary C-fibres initiates coughing: Cough receptors are insensitive to capsaicin and anaesthesia in contrast to bronchopulmonary C-fibres, lending support to the existence of parallel pathways regulating cough [7]. C-fibres originating from the lungs can be inhibitory to cough and so further research is needed to clarify their involvement in homeostasis versus a pathological state, and thus identification of potential therapeutic targets.

Members of the transient receptor potential (TRP) family, including TRP channel subfamily vanilloid member 1 (TRPV1), TRP channel melastatin member 8 (TRPM8) and TRP channel subfamily A member 1 (TRPA1), are expressed on airway sensory nerves, and are directly activated by mechanical, chemical and thermal stimuli [11]. For example, capsaicin stimulates bronchopulmonary C-fibres via the TRPV1 receptor [12]. The TRPV1 receptor also responds to other noxious stimuli including heat and low pH. TRPV1 is overexpressed in patients with chronic cough [13], and with severe asthma [14]. Of likely relevance also to interstitial lung diseases, TRPV1 and/or TRPA1 can be sensitised indirectly by a range of inflammatory mediators, including bradykinin, nerve growth factor and PGE2, which act by decreasing the TRP activation potential [15].

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TRPV1 activation triggers the release of neuropeptides mediating vessel dilatation and permeability, such as substance P and neurokinin A [16]. Furthermore, substance P and neurokinin may in turn induce activation and chemotaxis of fibroblasts, thereby contributing to the fibrotic process [17]. P2X2/3 receptors are also expressed on sensory afferents innervating the airways and are recognised as important in transducing signals from the lung periphery to the central nervous system including from the visceral pleura in animal models [18–20].

Perhaps surprisingly, no studies have yet been performed to address the distribution or response to activation of the TRP family or P2X2/3 receptors in pulmonary fibrosis. This is clearly an area that requires dedicated research, given the heavy burden of cough on quality of life of patients with ILD.

2. Cough in interstitial lung disease

Cough in the context of interstitial lung disease has not been the focus of many studies [21]. From the >300 existing ILD entities, for the purpose of this review, we have chosen to highlight only a few of the more frequently encountered conditions including: Idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis and systemic sclerosis associated ILD.

2.1. Idiopathic pulmonary fibrosis (IPF)

Idiopathic pulmonary fibrosis (IPF) is the most frequent of the idiopathic interstitial pneumonias (IIPs), causing more than 5000 deaths each year in the UK alone [22,23]. It is more common in older men with a history of cigarette smoking. IPF is a dismal disease, characterised by progressive parenchymal distortion and scarring, with a median survival of only 3 years, although a wide variability in disease course is increasingly recognised [23]. Histologically, IPF is defined by a usual interstitial pneumonia (UIP) pattern, characterised by temporal and spatial heterogeneity, fibroblastic foci and areas of microscopic honeycombing, dilated airspaces surrounded by fibrosis [24]. IPF is thought to result from the complex interaction between genetic susceptibility, increasingly well defined [24–27], and environmental insults, with cigarette smoke the most powerful environmental risk factor described to date [28]. Recurrent micro-injuries to the alveolar epithelial cell are believed to initiate a cascade of events leading to a progressive fibro-proliferative response [29–31].

More than 80% of patients with idiopathic pulmonary fibrosis suffer from chronic cough [21]. Ryerson et al. compiled a prospective database of 242 patients with IPF and examined the clinical associations and prognostic value of cough. Intriguingly, cough was more common in never smokers as well as in individuals with more advanced disease, and was found to be an independent predictor of disease progression [32]. Similar to other respiratory conditions [33,34], cough in IPF occurs predominantly during the daytime. [35]. This may well be due to the fact that sleep itself is potently inhibitory to cough [36].

In IPF, intractable cough [37,38], in addition to disabling shortness of breath [39], has a major impact on quality of life and should not be underestimated. Health-related quality of life measures provide invaluable information in addition to physiological parameters and are increasingly employed in research as part of a drive towards targeting of patient-centred outcomes in what is a debilitating and extremely challenging condition to treat.

It may seem somewhat surprising that cough is such a prominent symptom in patients with IPF, a disease which has been traditionally thought to exclusively involve the alveolar interstitium, where neuronal innervation is sparse. However, there are a number of mechanisms which are likely to play a role in the pathogenesis of cough. The striking genetic association between a promoter polymorphism in the MUC5B gene (encoding one of the main airway mucins) and both familial and sporadic IPF, and the overexpression of MUC5B in the small airways and honeycomb cysts in IPF [26,40–47], highlights a role for the peripheral airways in IPF which had been hitherto under-recognised. Interestingly, the minor (T) allele is associated with a greatly increased risk of IPF, but is also linked to a slower rate of decline [42] and improved survival [29]. Interestingly, the increased expression of MUC5B in distal airways is not observed in fibrotic NSIP pattern, whether idiopathic or associated with scleroderma, suggesting that this mechanism is specific to IPF [48]. Whether the MUC5B variant is also associated with an increased prevalence of cough as suggested by Scholand et al., will require further confirmatory studies [49]. Proliferation of bronchiolar cells specific to IPF compared to other ILD patterns had been originally reported by Chilosi et al. [50]. Very recent studies further support a key role for bronchiolar proliferation/small airway involvement in IPF [51,52].

Up-regulation of the neurological pathways of cough is likely to play a crucial role. Heightened cough reflex to inhaled capsaicin and substance P, independent of volume restriction, is observed in patients with IPF [53,54] and is paralleled by elevated levels of neurotrophin factors, nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), in induced sputum [54] and immunostaining of lung tissue [55], suggesting upregulation of sensory C-fibres and/or a lowered threshold to neuronal stimulation of the cough reflex in more proximal airways, giving rise to the concept of airway neuroplasticity [29,56]. The recent discovery of an altered lung microbiome in patients with IPF [57] could suggest epithelial disruption and sensory nerve exposure as another potential mechanism for an exaggerated cough response, as has been observed in otherwise healthy Japanese subjects exposed to substance P following an upper respiratory tract infection [58].

Additional mechanisms are likely to include traction bronchiectasis, a dilatation of the larger airways associated with surrounding fibrosis, easily identified on CT, linked to alterations to the structure of the airways which could significantly contribute to cough pathogenesis. Mechanical chest wall percussion using a cutaneous electrical oscillator has also been shown to induce cough in patients with IPF compared to healthy controls, in particular when applied to the basal zones, which are preferentially involved [59]. These observations support the hypothesis that architectural distortion of the bronchial tree may either sensitise or upregulate mechanical sensors of the cough reflex arc or disrupt cough-inhibitory C-fibre subtype neuronal pathways, resulting in an exuberant coughing response in these individuals [29].

2.2. Granulomatous ILD

2.2.1. Sarcoidosis

Sarcoidosis is a condition characterised by non-caseating granulomatous inflammation in the absence of an infective or infiltrative cause [60]. The prevalence of sarcoidosis is 10–20 per 100,000 individuals and more commonly occurs in the Afro-Caribbean population [61,62]. A genetic predisposition (HLA DR 11, 12, 14, 15, and 17) [63,64] and environmental triggers (infections for example, propionibacterium and mycobacterium, and various organic/inorganic agents) [60,63] have been implicated by association. Sarcoidosis presents with an extensive range of symptoms reflecting the potential for multisystem involvement.

Pulmonary involvement is observed in over 90% of patients with sarcoidosis and can affect both the upper and lower respiratory tracts [65]. The prevalence of cough is estimated at between 30 and 50% [56]. The pathogenesis of cough is thought to mainly relate to a combination of parenchymal involvement leading to airway distortion, and granulomatous mucosal inflammation causing airflow limitation and hyper-responsiveness [21,66,67]. Indeed, sarcoid granulomas