NERVES, COUGH, AND IDIOPATHIC PULMONARY FIBROSIS

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias. It has a poor prognosis with a median survival of approximately 3 years, and whilst new therapies are finally beginning to offer hope of improved survival, most patients will require palliation of symptoms as their disease progresses. Whilst all patients with IPF complain of breathlessness, up to 80% develop a distressing cough, which is detrimental to their quality of life and difficult to treat. This article examines the possible causes of cough in the wider context of current theories of the pathogenesis of IPF and its associated comorbidities, which may also cause or exacerbate cough. We examine the evidence for increased cough sensitivity in patients with IPF and neuroplasticity in animal models of lung pathology. Finally, we discuss new therapies that are becoming available to treat cough in IPF and their possible mechanisms of action, and which highlight the need for further, appropriately powered studies that include objective measures of cough as an outcome.

Keywords: Idiopathic pulmonary fibrosis (IPF), pathogenesis, cough, therapy.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and invariably fatal lung disease and the commonest of the idiopathic interstitial pneumonias (IIPs). In the UK, the annual incidence is approximately 4.6 cases per 10,000 individuals and is increasing by 5% per annum, a trend mirrored by hospital admission rates. Patients who develop IPF usually present with symptoms of progressive breathlessness. Interestingly, up to 80% also complain of cough, which is either dry or productive of scanty amounts of clear sputum. Cough as a symptom is most commonly associated with inflammatory conditions such as asthma, bronchitis, and viral infections affecting the airways where sensory innervation is extensive. However, cough is also prevalent in a number of IIPs. In some, such as hypersensitivity pneumonitis and sarcoidosis, it is likely to result from granulomatous inflammation of the airways, although sarcoidosis may also involve the upper respiratory tract, which has exquisitely sensitive innervation. Superficially, it seems anomalous that a symptom such as cough should be associated with IPF - a disease process predominantly affecting the lung parenchyma where sensory innervation is relatively sparse. In this regard, an analogy may be drawn with asbestosis, a fibrotic lung disease with a defined cause that resembles IPF in its clinical presentation and in which cough is also a common symptom.

The histological pattern observed in IPF is termed usual interstitial pneumonia and is characterised by excess collagen and other molecules of the extracellular matrix (ECM) within the alveolar interstitium, together with a modest inflammatory cell infiltrate. These changes typically demonstrate spatial and temporal heterogeneity, giving the impression that the lung has been subject to recurrent micro-injuries. Thus, areas of relatively normal lung are interspersed with areas of mild fibrosis, yet other areas show extensive fibrosis with subpleural, 3-10 mm mucin-filled cysts lined with bronchiolar epithelium, termed honeycombing.
The latter, which can be demonstrated using computed tomography (CT) scanning of the thorax, is typically worse at the posterior lung bases and spreads medially and cephalad as the disease progresses (Figure 1). Extensive disease is also characterised by subepithelial knots of mesenchymal cells and matrix situated at the interface between normal and fibrotic lung termed ‘fibroblastic foci’. This article will concentrate on what is known about cough in the context of current theories on the pathogenesis of IPF.

**THEORIES ON THE PATHOGENESIS OF IPF**

The precise pathogenesis of IPF remains unclear but an increasing body of evidence suggests that it arises as a result of recurrent micro-injury to alveolar epithelial cells (AECs). It is known that injured AECs release mediators including platelet-derived growth factor and transforming growth factor-beta (TGF-β), which stimulate interstitial fibroblasts to proliferate into myofibroblasts and secrete ECM. Furthermore, these myofibroblasts themselves secrete TGF-β, which has a number of effects. Firstly, it causes apoptotic cell death of AECs, thereby perpetuating a process of aberrant wound healing. In addition, it can initiate epithelial–mesenchymal cell transition (EMT), whereby epithelial cells de-differentiate and take on characteristics of mesenchymal cells.

Myofibroblasts are also capable of secreting tissue inhibitors of metalloproteases, which have the profibrotic effect of impairing matrix degradation. Thus, TGF-β is a key mediator in the crosstalk between epithelial cells and the mesenchymal cells responsible for matrix deposition and fibrosis of alveolar walls. For a more detailed review of these mechanisms see publications by Kage and Borok, and Fernandez and Eickelberg.

Genetic susceptibility is also thought to play a role in the pathogenesis of IPF, and mutations in genes encoding the surfactant proteins C and A2 as well as those maintaining telomere length are now known to be associated with IPF. Familial IPF, defined as disease occurring in two or more family members, is estimated to account for 3.5% of cases. More recently, a common polymorphism in the promoter for the gene MUC5B, encoding the mucin 5B which is important in innate immune defence, has been noted to have a high prevalence in familial (34%) and sporadic (38%) IPF. This is one of very few examples of a common variant with a very large genetic effect, since each copy of the mutant allele confers a 1.6 to 8.3-fold increase in the risk of developing IPF. Interestingly, the presence of this polymorphism, whilst associated with increased risk of developing the disease in a dose-dependent manner, also confers improved survival. Genetic variants in the TOLLIP gene, a regulator of the pattern recognition Toll-like receptors and the TGF-β Type 1 receptor, located on the same genetic locus as the MUC5B gene, may also be associated with IPF.

The increasing evidence that susceptibility to IPF involves genes important in innate immunity has given new momentum to the theory that infectious agents in the lower respiratory tract (LRT) may contribute to the initiation or progression of IPF. Recently, the polymerase chain reaction has been applied to define the respiratory microbial flora and their genes, the ‘microbiome’ of IPF, and differences in the quantity and relative abundance of bacteria, specifically Haemophilus, Neisseria, Streptococcus, and Veillonella, have been observed. There is also evidence that this greater bacterial burden is associated with rapidly progressive disease.

A completely different hypothesis that attempts to link the histopathological features of IPF with recurrent stretch injury, caused by tractional forces on the lung parenchyma exerted by the pressure changes during breathing, was recently suggested.
It is known that these forces are greatest at the pleural surface of the lung bases where the lung is more susceptible to alveolar collapse, a location where IPF is first evident radiologically and usually most severe (Figure 1). Leslie argues that the combination of mechanical force and alveolar collapse may cause lines of sheer stress, which fracture the epithelial—mesenchymal interface. Such injuries would then lead to fibroblast activation and healing in a ‘reticulum of repair’, thus explaining why fibroblastic foci are not discrete entities but part of a three-dimensional meshwork within the peripheral lung. Other factors contributing to such injury might include inherited surfactant deficiencies and an ageing lung modified by environmental agents such as cigarette smoke.

**PATHOPHYSIOLOGY OF COUGH**

The cough reflex plays a vital role protecting the respiratory tract from inhaled noxious agents. The sensory fibres forming the afferent limb of this reflex are located in the vagus nerve, which innervates the larynx, trachea, and branching points of proximal airways. The afferent part of the reflex involves rapidly adapting receptors (RARs) and slowly adapting, or unmyelinated, C-fibres. RARs are myelinated Aδ nerve fibres that have their cell bodies in the nodose ganglion and are exquisitely sensitive to changes in pH, osmolality, and mechanical stimulation. However, they lack transient receptor potential vallinoid 1 (TRPV-1) receptors and are thus not chemosensitive. Stimulation of these fibres in anaesthetised animals evokes a violent cough response, illustrating the involitional nature of this primarily protective reflex. Unmyelinated C-fibres have their cell bodies in the jugular ganglion and unlike RARs are responsive to chemicals including the TRPV-1 agonists capsaicin and bradykinin. Inhalation of these substances causes an unpleasant, itchy ‘urge to cough’ experienced in many disease states.

The afferent fibres emerge from the nodose and jugular ganglia to converge on sites in the nucleus tractus solitarius in the brainstem. From here they connect to neurons in the central respiratory generator, which co-ordinates the efferent motor response in the larynx, diaphragm, and intercostal muscles. However, neurons in the cerebral cortex can also influence cough that can, in part, be voluntarily induced or suppressed. These higher cortical sites can be demonstrated using functional magnetic resonance imaging following inhalation of capsaicin. It is increasingly recognised that neuroplasticity, whereby nerves switch phenotype, can occur in a number of pathological processes. Animal models have demonstrated altered tachykinin expression in tracheal Aδ fibres following viral infection, and allergic inflammation can induce a switch with respect to the TRPV-1 receptor. How such neuroplasticity may have relevance to cough in IPF will be discussed in the following section.

**COUGH IN IPF**

When asked to describe their cough, patients with IPF report having a ‘nagging desire to cough constantly’ and ‘never being relieved after coughing’. A recent study using a validated cough counter showed that patients with IPF cough as frequently as patients with cough hypersensitivity syndrome and significantly more than asthmatics. Interestingly, cough in IPF is more prevalent in never-smokers and patients with advanced disease, and there is evidence that it is an independent predictor of disease progression and may predict time to death or transplantation. The cough of IPF is also known to be associated with a variety of adverse physical and social sequelae, which have a profound and deleterious effect on quality of life. A major obstacle when studying the pathogenesis of cough in IPF is the frequency of confounding comorbidities, which can both independently cause cough and/or have been proposed as potential pathogenic mechanisms that may initiate or lead to the progression of IPF. These are listed in Table 1 and discussed below.

**Table 1: Common comorbidities in idiopathic pulmonary fibrosis.**

| Gastro-oesophageal reflux | Obstructive sleep apnoea |
| Sinusitis/upper airway cough syndrome | Emphysema |
| Angiotensin converting enzyme inhibitor therapy | |
COMORBIDITIES

Gastro-Oesophageal Reflux Disease

The first objective evidence that gastro-oesophageal reflux disease (GORD) is associated with IPF came from a study that used oesophageal pH monitors to demonstrate that acid reflux into the distal oesophagus was greater in patients with IPF than controls. A number of subsequent studies have confirmed this observation and it is now accepted that up to 80% of patients have acid reflux, which may be asymptomatic.

It is increasingly appreciated that gastric refluxate may be gaseous as well as liquid and also contains pepsin, duodenal enzymes, and bile. There is preliminary evidence that exposure of airway epithelium to pepsin can result in EMT as discussed earlier, whilst in the presence of unconjugated bile salts, AECs have been shown to produce TGF-β. A recent study found detectable pepsin in the bronchoalveolar lavage (BAL) fluid of 54 patients with IPF, but there was no difference in the mean BAL pepsin levels between clinically stable patients and those undergoing an acute exacerbation. However, a subgroup undergoing an acute exacerbation had markedly elevated levels of pepsin suggesting that aspiration may be contributory in some cases. It is also noteworthy that in rodent models, chronic aspiration of pH-neutralised gastric fluid produced a similar pattern of injury to acidic gastric fluid, whilst aspiration of acidic solution (hydrochloric acid) did not, suggesting that if reflux does play a role, it is not the acidity of the aspirate that is important. This is supported by data from a recent, interventional study in which high-dose acid suppression using proton pump inhibitors (PPIs) reduced acid reflux in IPF patients but paradoxically increased non-acid reflux and had no impact on cough counts.

Obstructive Sleep Apnoea

A number of recent observations have suggested that IPF may be associated with sleep-disordered breathing. A single-centre study of 50 patients with IPF who had a high mean body mass index of 32.3 found that 68% had moderate or severe obstructive sleep apnoea (OSA). A further study observed that one-third of patients with OSA reported symptoms of chronic cough. Interestingly, GORD is common in OSA and proportional to its severity. There is also strong epidemiological evidence linking these two conditions. It is therefore possible that IPF, GORD, and OSA are associated in what has been termed a ‘vicious triad’ provoking cough. However, not all evidence supports this notion. A single-centre study of 54 patients with fibrosing interstitial lung disease, many of whom had IPF, used polysomnography and oesophageal probes to demonstrate that reflux was no more prevalent or severe in subjects with OSA when compared with subjects without OSA. Thus, current evidence suggests that confounding comorbidities alone are insufficient to explain cough in all patients with IPF and other possible mechanisms should be considered.

INCREASED COUGH SENSITIVITY IN IPF

It is known that patients with IPF have enhanced cough reflex sensitivity to inhaled capsaicin and that induced sputum from patients with IPF contains higher levels of the neurotrophins nerve growth factor and brain-derived neurotrophic factor (BDNF) than controls. Furthermore, immunohistochemical studies have demonstrated that bronchial epithelial cells, subepithelial mesenchymal cells, and alveolar macrophages in normal human lung stain for neurotrophins and their receptors. In IIPs, this expression is enhanced particularly in IPF (Figure 2), where fibroblastic foci express high levels of BDNF and its receptor.

Figure 2: Alveolar macrophages in a lung biopsy from a patient with idiopathic pulmonary fibrosis show strong immunostain for nerve growth factor.
It has been proposed that these neurotrophins may induce the previously mentioned neuroplasticity by stimulating proliferation or differentiation of more proximal sensory nerves, resulting in increased cough reflex sensitivity. Interestingly, a preliminary study of alveolar macrophages obtained from patients with IPF by BAL showed enhanced expression of messenger RNA for nerve growth factor when cultured in vitro with lipopolysaccharide compared with macrophages in culture medium alone (Figure 3). These data, taken together with the aforementioned abnormalities in the microbiome of patients with IPF, provide a possible mechanism by which the LRT provides an environment that enhances upregulation of neurotrophins, neuroplasticity, and a lower cough threshold.

BIOMECHANICAL FACTORS AND COUGH IN IPF

It has long been recognised that histological abnormalities of IPF extend beyond the alveoli to include peribronchiolar fibrosis with resultant distortion of distal airway anatomy. This is evident as traction bronchiectasis, which can be easily demonstrated on CT scanning (Figure 1). Commensurate with this observation and the previously discussed tractional injury hypothesis is the notion that mechanical distortion of the lung in IPF might directly alter sensory innervation either by increasing the number or sensitivity of mechanosensitive RARs, or conceivably, by destruction of nerves that inhibit the cough reflex. A recent study provided evidence to support this hypothesis by demonstrating that mechanical stimulation of the chest wall, particularly over the lung base where fibrosis is extensive, could induce a ‘vibration cough’ in patients with IPF but little or none in controls. If this theory is correct, it would explain why patients with IPF cough when talking, as the enhanced transmission of vibration caused by phonation (as with tactile vocal fremitus) would increase mechanical stimulation of pulmonary sensory receptors. Indeed, vibration produced by the sound of cough might itself perpetuate further cough by a positive feedback mechanism.

Figure 3: Alveolar macrophages from a patient with idiopathic pulmonary fibrosis show a time-dependent upregulation of messenger RNA (mRNA) for nerve growth factor (NGF) after stimulation with lipopolysaccharide (LPS).

*p<0.001.

Courtesy of Dr Mat Jones and Jones RM.
**TREATMENT OF COUGH**

Treatment of IPF-associated cough is often unrewarding for the patient and clinician. With regard to specific antitussive therapy, national guidelines recommend the use of opiate-based pharmacological agents, although these are often of only modest benefit and have unwelcome side-effects. However, in patients with severe fibrosis and distressing cough, morphine can be an important part of palliative care. Clearly, it is important to address any of the possible comorbidities outlined in Table 1 that might be amenable to therapeutic intervention. In particular, if patients have symptoms of GORD, treatment with optimal doses of PPIs should be offered and supplemented if necessary with other antacid therapies and prokinetic agents. Interestingly, retrospective studies have shown prolonged survival in patients given antacid therapy; a recent study that analysed change in forced vital capacity (FVC) in patients assigned to placebo arms of three large randomised controlled trials found that patients taking antacid therapy at baseline had a smaller decrease in FVC at 30 weeks, compared with those not taking antacid therapy.

It is also important to recognise that cough is a symptom that is notoriously susceptible to improvement with placebo, hence results of inadequately controlled clinical trials should be interpreted with caution. A recent 24-week, double-blind, two-treatment, two-period crossover study showed a benefit of thalidomide as determined by visual analogue score, a cough specific questionnaire, and the St George’s Respiratory Questionnaire. These results are encouraging and it is interesting to speculate on the possible mechanisms by which thalidomide might exert its action. Whilst it is known that thalidomide has anti-inflammatory and anti-angiogenic effects, its side-effects include dizziness, peripheral neuropathy, and anti-cholinergic effects — actions which, taken with its apparent speed of onset, suggest that it could have a direct effect on pulmonary sensory nerves.

Until recently, there was no therapy proven to improve outcome in IPF. However, the anti-fibrotic agent pirfenidone and the tyrosine kinase inhibitor nintedanib have both been recently shown in randomised controlled trials to slow the rate of deterioration in lung function in patients with IPF, particularly those with relatively mild disease. Whilst none of these studies included cough as an endpoint, one trial employed a simple, four-point cough severity score. When all patients were included, pirfenidone had no significant effect on cough. However, whilst post-hoc, subgroup analysis should be interpreted with caution, the authors identified a subgroup of patients whose cough appeared to benefit (i.e. deteriorate less) from high-dose pirfenidone. Interestingly, pirfenidone has been shown to reduce cough in a guinea pig model of cough induced by ovalbumin sensitisation and capsaicin challenge. This effect was associated with a reduction in BAL prostaglandin E$_2$, leukotriene B$_4$, and substance P, all molecules thought to enhance cough sensitivity in the airways. Less is known about the effect of nintedanib on cough. However, on comparing cough as a self-reported adverse event in the IMPULSIS trial, there was no statistical difference between those receiving nintedanib and those receiving placebo.

**CONCLUSION**

Whilst our understanding of the pathophysiology of IPF has improved greatly in the last decade, the precise mechanisms remain elusive. IPF likely involves a complex interplay between genetic factors, environmental insults, EMT, and crosstalk with mediators such as TGF-$\beta$. The contributory weighting of each component may vary with individual patients, but combined, these factors culminate in the distinctive, common pathological changes of usual interstitial pneumonia. Similarly, the distressing cough patients suffer may be a cumulative manifestation of a multitude of disease-related mechanical, biochemical, and neurophysiological changes within the lung, perhaps in some cases exacerbated by associated comorbidities. Recent trials of promising, disease-modifying drugs are now providing new hope for patients with IPF. Rigorous study of cough in IPF may help achieve more targeted and effective symptomatic therapies and provide further insight into its pathogenesis. Given that cough is such a ubiquitous and disabling symptom in this disease, it is essential that validated, objective measures of cough are included as outcome measures in future clinical trials.
REFERENCES


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