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Pathophysiology and Pharmacotherapy of Persistent Post- Infectious Cough: A Review of Literature

* Lavina Prashar and Christian C Ezeala

Division of Pharmacology, Department of Physiological Sciences, School of Medicine, University of Zambia, Lusaka, Zambia

***Corresponding author e-mail:** prasharlavina@gmail.com

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ABSTRACT

Persistent post-infectious cough (PPC) is a subacute cough lasting less than 8 weeks. This article aims to review recent advances in the pathophysiology and pharmacotherapy of PPC secondary to upper respiratory tract infection. Between April and August, 2016, relevant databases were searched using the search words "subacute cough," "persistent post-infectious cough," "post-viral cough," "causes," pathogenesis," and "management." Inflammatory mechanisms play a reported role in the pathophysiology of PPC. Interplay of mediators such as neuropeptides, cysteinyl leukotrienes, Th1-like and Th2-like cytokines and gamma interferon, has been suggested. Combination of 'Honey and 'Coffee' and Suhuang Zhing, a traditional Chinese medicine is reported to demonstrate clinical efficacy in clinical trials. Natural products and herbal medicines appear to be superior to conventional treatments.

Keywords: Persistent post-infectious cough, upper respiratory tract infections and natural remedies.

INTRODUCTION

Cough is a common symptom observed in many diseases other than those affecting the respiratory system. It may be arbitrarily referred to as: [1]
Acute: if it lasts maximum of 3 weeks
Sub acute: if it lasts 3-8 weeks.
Chronic: if it lasts more than 8 weeks.
Persistent post-infectious cough (PPC) is classified as sub-acute cough as the episode lasts not more than 8 weeks. Specific infectious etiology of PPC is rarely confirmed. Respiratory Syncytial Virus (RSV), Adenovirus, Parainfluenza virus, Influenza virus etc have been implicated. Persistent post-infectious cough, following an upper respiratory tract infection (URTI) secondary to viral infections accounts for 11-25% of all cases of sub acute cough. [2] Viral causes require to be differentiated from other non-viral causes e.g. Mycoplasma pneumonia, Chlamydia and Bordtella pertusis which may require more specific treatment and are commonly encountered in children.[3,4] Persistent post-infectious cough also requires to be differentiated from other non-infectious causes of cough including gatro-oesophageal reflux, aspiration, bronchial asthma, sub-clinical congestive heart failure, post-nasal drip syndrome (upper airway cough syndrome) and rarely; pulmonary sequestration, tourette's syndrome.[1]

Multifactorial pathogenesis and self limiting nature of PPC, results in a diagnostic challenges.[5-7] Prospective studies have shown that in unselected patients, many of whom had upper respiratory tract infection, post infectious cough was not diagnosed corresponding to the low frequency of prevalence.
[4]Bacterial infections is said to play no role in the pathogenesis of PPC in adults and therefore antibiotics are said to be ineffective in its treatment. [8] Accumulating evidence from the past two decades suggests that non diagnosis of PPC which is self limiting in nature has resulted in overprescribing of antibiotics, corticosteroids, cough suppressants

(dextromethorphan), decongestants (pseudoephedrine), expectorants (guaifensin) and anti-histamines (chloropheniramine) which not only increases annual prescribing costs but also results in increased incidence of adverse drug reactions, bacterial resistance.[4,9]

Patients continue to be attended by primary care practitioners and often present after the acute illness has settled but the cough remains. Lack of treatment options available and no investigations based pathological changes poses a management challenge of such patients. This causes profound emotional distress for the medical practitioner managing such patients.

The aim of this systemic review is to evaluate the pathogenesis and developments in the management of PPC following upper respiratory tract infection.

METHODS

Research Protocol: The research was conducted based on predefined unpublished criteria inclusive of; research questions, search data base, inclusion and exclusion criteria.

Research Questions:

What is the pathophysiology of persistent post-infectious cough?

What are the symptoms of persistent post-infectious cough?

What are the treatment options for the management of persistent post-infectious cough?

Objectives:

To present current evidence on the pathogenesis and pathophysiology of persistent post- infectious cough secondary to viral URTI.

To present current opinions on the pharmacological treatment of persistent post infectious cough, including the use of natural products.

Database and Search Engines: A thorough literature search was conducted in the main international search databases including; Pubmed, Embase, Medline and Cochrane register of Controlled trials. The search was conducted through April - August 2016, of all articles inclusive of original clinical trials and reviews published in English. Selected bibliographies of identified studies were also searched. For this search the key words used included, 'sub-acute cough', 'persistent post-infectious cough', 'post viral cough', 'post-influenza cough', 'post-cold cough', 'causes of persistent-post infectious cough', 'pathogenesis of post infectious cough', recent advances in management of persistent post-infectious cough'.

Eligibility: All studies/ articles/review articles/placebo and non-placebo controlled randomized trials with the required information on PPC in adults following URTI.

Studies on 'cough' with no specific relation to 'persistent post-infectious cough', were excluded.

Studies on other differential causes of, 'sub-acute cough' inclusive of, asthma, upper airway cough syndrome (UACS), gastro esophageal reflux disease, other underlying cardio-respiratory illness, were excluded unless they included comparison to, persistent post-infectious cough. Also excluded were studies on, chronic cough.

Types of intervention: All types of interventions for management of PPC; herbal and non-herbal, comparative and non-comparative; were included. The documentation was irrespective of the dose used, dosage form, duration or route of administration. Quality assessment of randomized controlled trials were not undertaken.

Outcomes: The primary outcome measures to interventions were inclusive of the following but not limited to:

Primary outcomes: Severity and duration of cough based on self reported scoring systems including Likert scale and Visual Analogue Scale. [10]

Severity and duration of cough based on objective measures e.g. ambulatory cough counts using audio-recording devices and subsequent interpretation using soft-ware packages. [11]

Secondary Outcomes: Quality of life (QoL) score evaluated using Cough – Specific Quality-of-Life Questionnaire (CQLQ) or Leicester Cough Questionnaire (LCQ), [11-13] overall cough severity, paroxysmal cough severity, cessation of cough, cessation of exercise induced cough,[10] Adverse events. [14]

RESULTS and DISCUSSION

Pathophysiology: The pathogenesis of post viral persistent post-infectious cough is not known, but is said to be long-lasting and multifactorial.[4] Central to its development is thought to be the widespread transient pharyngeal mucosal inflammation and desquamation of the epithelial cells leading to 'nerve end damage' that result in, 'hyper responsiveness of airways' and 'impaired muco-cilliary clearance'. Airways inflammation also results in hypersecretion of mucus. Retained secretions drain into the hypo-pharynx and larynx and stimulate the receptors of cough. [4, 15] Bronchoscopy and biopsy performed on patients' by Zimmerman, [16] revealed extensive

desquamation of epithelial cells to the level of the basement membrane. The bronchalveolar lavage (BAL) fluid of these patients was found to be rich in lymphocytes and neutrophils; eosinophilic inflammation which is typical of asthma was absent. [16]

In a comparison study done on the sensitivity of cough receptors, heightened sensitivity to inhaled capsaicin and tartaric acid was seen in patients with 'post-viral' persistent cough but not in patients in the acute and convalescent phases of post infectious cough due to Mycoplasma pneumonia. The sensitivity returned to normal only after 4 weeks. [17] Hyper responsiveness decreases the cough threshold and increases susceptibility of the cough reflex to factors like cigarette smoke, aerosol sprays, chemical fumes, perfumes, dust, drinking, eating, talking, laughing and breathing cold air. [2] Vigorous coughing may lead to gastro-esophageal reflux-disease or worsen it. The gastro-esophageal reflux may in turn worsen the persisting cough forming a vicious cycle. [4]

Cysteinyl leukotrienes, may be the contributing factors as they facilitate intra-thoracic and extra-thoracic inflammation in, RSV, Influenza A (H1N1) and Rhino virus, infected animal models. [18-20] Increased levels of cysteinyl leukotrienes have also been found in nasal secretions of humans. [21] Cysteinyl leukotrienes promote airway inflammation by activating pulmonary dendritic cells and potentiating the effects of inflammatory neuropeptides.[22, 23] Post-RSV infected bronchial; epithelial cells, mast cell membranes, vascular endothelial cells and T lymphocytes, have induced expression of 5 Lipo-oxygenase (5LO) genes and of Substance P (Nk1) receptor. Both mediators are known to interact and facilitate the vascular events of inflammation.[18, 24, 25] In rats, Montelukast, potentially inhibited neurogenic inflammation of intrapulmonary airways, leading to the speculation that leukotrienes may be released via mast cell- nerve interactions that are amplified during RSV infection and in turn, potentiate the inflammatory effects of neuropeptide like substances (Sub P). [25]

Viruses affecting the respiratory system are known increase production of interferon γ which increases the sensitization to leukotrienes thereby increasing the expression of cysteinyl leukotriene type-1 receptor. [19, 26] In adults rhinovirus infection activates both Th1 and Th2 like cytokine responses. TH 2 cytokine responses are said to be associated with delay in clearance of the virus from the sputum and also contribute to increased duration of inflammation of the respiratory tract and severity of symptoms. [27] Intra thoracic hyper-responsiveness is a recognized mechanism for post-infectious cough. Extrathoracic airway hyper-responsiveness was indicated as a possible mechanism in recent studies. [6, 28, 29].Teran et al., [28] postulated paradoxical vocal cord dysfunction (PVCD) as a cause of persistent post-infectious cough. PVCD may occur as a consequence of upper respiratory tract infections with viruses causing cytopathic effect, neural activation, vagal nerve injury and inflammation in extra-thoracic airways. The pathogenesis seems to involve interplay of various inflammatory mediators, inclusive of but not restricted to, neuropeptides, Th1 and Th2 immunity, increased cysteinyl leukotriene concentrations and dendritic cells in the lung tissue. [23]

Diagnosis/Symptomatology:

Persisting cough that lasts for over 3 weeks following an URTI, and is not complicated with pneumonia; the chest radiograph remains normal and it ultimately resolves without treatment. [8] PPC does not result in any disability or mortality but does result in significant morbidity. The diagnosis of PPC is therefore clinical and based on exclusion.

Treatment:

The cough is self- limited and requires no specific treatment. Antibiotics may only be useful in bacterial sinusitis or early on in bacterial infections. [8]

Antihistamines, narcotics, centrally acting antitussive agents such as codeine, dextromethorphan and bronchodilators [4, 6, 30] are regularly used though deficiencies in the understanding of patho-physiological mechanisms have led to lack of controlled scientific evidence for use of such drugs. Holmes et al., [31] in a controlled double-blind, cross-over trial on 14 non-smoking patients with persistent post-viral infective cough, found that inhaled ipratropium bromide (4 puffs of 20µg, four times daily) resulted in overall clinical improvement and reduction in cough scores. The findings were however non -conclusive due to lack of a well designed trial.

Corticosteroids have been used over years for their anti-inflammatory properties to treat respiratory tract infections (RTI), such as croup, sore throat, pneumonia and also for asthma. Gohary et al., [11] in their review found only two adequately powered trials on use of corticosteroids for sub-acute cough. These studies did not show any positive role for corticosteroids in persistent post-infectious cough, nevertheless adequately powered research to determine the benefits and drawbacks of use of corticosteroids was recommended. Similarly

fluticasone and budesonide as inhaled coriticosteroids were ineffective in treating persistent cough. [32, 33] On the contrary, Gillissen, [34] and his team in their placebo controlled randomized study found treatment with inhaled extra-fine Hydrofluoroalkanes–beclomethasone diproprionate (HFA-BDP) resulted in a greater reduction of cough frequency in patients with persistent post-infectious cough. The suggestion was HFA-BDP autohaler produces extrafine aerosol particles resulting in higher lung deposition of BDP and an improved distribution into the smaller airways [35]. To further define the role of cysteinyl leukotrienes in the pathogenesis of persistent cough, a double -blind randomized placebo controlled trial using Montelukast was conducted [10]. Montelukast was found to be ineffective in the treatment but further trials are recommended, since montelukast demonstrated potential inhibition of neurogenically mediated inflammation of intrapulmonary airways in RSV infected animal models. [25]

The demonstration of role of neuropeptides in facilitating the hyper-responsiveness, indicates possible positive effects of inhibitors of neuro-peptide release, e.g. by cromoglycate or blockade of neuropeptide receptors e.g. by nedocromil. Fontana et al., [29] evaluated the effects nedocromil sodium administration in a placebo-controlled study on healthy subjects and found a significant increase in cough threshold values. For conclusive results on role of leukotrienes and neuropeptides further research is recommended. [10, 29]

Inconclusive results with standard synthetic drugs for PPC, have led to, an increasing number of clinical trials using natural and herbal remedies. In a double blind randomized controlled trial from 2008 to 2011, the participants were distributed in three groups, receiving respectively; ‘original instant coffee’, ‘honey’, ‘instant coffee and honey’. ‘Honey with coffee’ was found to be most effective treatment modality [36]. Two years later Raeessi [37] and his team compared the outcome of use of, ‘honey and coffee’ with, ‘prednisolone’, and ‘guaifenesin’. Main outcome measure was the mean cough frequency before and after one week’s treatment calculated by a validated visual analogue cough questionnaire score. The study concluded that, ‘honey and coffee’ is a better treatment modality than steroids for post-infectious cough. Similar results were seen when Raeessi and the team included and followed a larger pool of patients (245). [36]

Several mechanisms of action of, ‘honey and coffee’ have been proposed. Honey causes reflex stimulation of saliva and mucus secretion and improve mucocilliary clearance in the airways. It is hyper-osmolar and leads to demulscent effects in the pharynx.

Honey, reduces, release of prostaglandins and increases, nitric oxide release at site of inflammation. It has anti-inflammatory and anti-oxidant properties. Honey also reduces edema and stimulates epithelialization stages, tissue regeneration and improves granulation and debridement [38, 39]. Kamaruzuman N.A. et al., [40] demonstrated anti-inflammatory effects of aerosolized honey in rabbit models of asthma. Aerosolized honey in these models resulted in structural changes of the epithelium, mucosa and sub-mucosa of the airways. Honey also reduced the number of airway inflammatory cells present in the BAL fluid and inhibited goblet cell hyperplasia.

Caffeine, a naturally occurring alkaloid found rich in coffee, falls under the class of methylxanthines, which are bronchodilator drugs [37]. Theobromine, a bitter alkaloid in cocoa plant and rich in chocolates has also shown positive results and is currently in late stage of development for the treatment of PPC. (BC 1036, Phase III). Theobromine as a methylxanthine has bronchodilator effects and inhibits inappropriate firing of the vagus nerve. [41]

In 2011, Nosalova et al., [42] identified an arabinogalactan-protein extract (composed of galactose and arabinose with low protein content) in instant coffee powder of Coffea arabica beans. This molecule demonstrated significant dose dependent in vivo anti-tussive and ex-vivo immunomodulatory activities. AGP induced pro TH1 inflammatory cytokines i.e. TNFα and IFNγ, which antagonize the cytokines of TH2 cells. TH2 cells and their cytokines as mentioned, participate in inflammatory process of airway-hyper-responsiveness.

The Traditional Chinese Medicine (TCM), theory system has its own definition of pathophysiology of persistent cough. [14] A systemic review on Chinese herbal medicine (CHM) for persistent post-infectious cough, suggested that Chinese herbal Medicine have potential positive clinical effect. Chinese herbal medicines used in the trials were in form of concoctions of various herbs e.g. Suhuang zhing capsule. Most commonly used herbs in these concoctions included; Ephedra, Platycodon grandiflorus, Folium perilla, Almond and Schizonepeta tenuifolia. The criteria for determining the outcome was based on the pathophysiology of PPC as defined by TCM. This review concluded that CHM have potential curative effects, show earlier anti-tiussive effects and are relatively safe. A met analysis of the ingredient most useful has to be

further tested. [14] A step forward to this is the Phase II trial underway using the TCM formula Qing-Feng-Gan-Ke-Granules. [43]

Speech pathology intervention, in a placebo-controlled trial, reflected a successful outcome in 88% of the patients with EAHR and symptoms of PVCM. Similarities in the pathophysiological mechanisms of EAHR and PVCM led Ryan NM and Gibson PG [44] to suggest the possible benefit of speech language therapy for post-infectious cough and recommended further evaluation.

CONCLUSION

Persistent post infectious cough is often misdiagnosed and treated as chronic cough in primary care settings. The patients are overloaded with antibiotics and anti-tussives, unnecessarily increasing costs and predisposing patient to a further burden of related side effects. PPC is a self-limiting disease lasting from 3-8 weeks but nevertheless increases morbidity. Several drugs have been tried but with inconclusive results. This has prompted an approach of trying natural remedies and this has shown some positive results, which require to be further investigated. Nevertheless inconclusive results still pave way for further trials, and require better understanding of underlying mechanisms of post-infectious cough.

CONFLICT OF INTEREST

The authors declare that no potential conflict of interest exists in preparing this document.

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