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Cough in sarcoidosis patients

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A B S T R A C T

Sarcoidosis is a multi-system disease of unknown aetiology characterized by presence of non-caseating granulomatous inflammation. Cough is a common and significant symptom in sarcoidosis, reducing quality of life. Objective 24 h cough monitoring proved that sarcoidosis patients have significantly higher cough frequency compared to controls and their cough has diurnal variation, it is gender-specific and shows racial differences. It correlates with the presence of inflammation in the airways, but is not influenced by the X-ray staging of the disease, nor the degree of airway obstruction.

Subjects with sarcoidosis have heightened cough reflex sensitivity, which is a result of interaction between the airway cough sensors and consequences of pathological process, detailed pathogenesis of cough in this demographic is unclear. The airway hyperresponsiveness, sarcoidosis of the upper airways and sensitivity to biomechanical forces play a role. More studies should be performed to understand pathogenesis of cough in sarcoidosis patients to improve the management of this troublesome symptom.

1. Introduction

Sarcoidosis is a multi-system disease of unknown aetiology characterized histologically by the presence of non-caseating granulomatous inflammation. Although any tissue of the human body can be affected, sarcoidosis typically affects hilar and mediastinal lymph nodes, the lung interstitium and bronchial epithelium. Diagnosis relies on a compatible clinical and radiologic presentation, the evidence of non-caseating granulomas, and exclusion of other diseases with similar findings, such as infections or malignancy.

Sarcoidosis occurs in people of all ages and races, most often before 50 years of age, with peak incidence between 20 and 39. Women are affected slightly more often than men. Incidence of sarcoidosis varies between different populations and ethnic groups (Kieszko et al., 2016). The annual incidence was reported to be as low as 0.73 per 100,000 in Japanese men to as high as 71 per 100,000 in African-American women (Ungprasert et al., 2016). The highest annual incidence is recorded in the Scandinavian countries, with about 50 cases per 100,000 residents (Kieszko et al., 2016).

In a recent study (Ungprasert et al., 2016), intrathoracic involvement was present in 97% of cases of sarcoidosis. In 87% of cases, this consisted of intrathoracic lymphadenopathy and 50% had evidence of pulmonary parenchymal infiltration, but only 43% had respiratory symptoms. This finding underscores the importance of chest radiographic imaging when the diagnosis of sarcoidosis is suspected, even in the clinically apparently asymptomatic patient.

Despite the fact, that this disease is known over one hundred years (Danbolt, 1958), aetiology is still not completely understood. It could be result of the interplay between different etiologic agents and the immune system in predisposed individuals (Beijer et al., 2017).

Genetic predisposition plays a key role. A positive family history was found in 6–19% of patient with sarcoidosis. Approximately 4–10% of patients have a first-degree relative with sarcoidosis (Rybicki et al., 2001). Predisposition to sarcoidosis is known to generally concern immunoregulatory genes (Spagnolo and Grunewald, 2013), genes regulating various aspects of angiogenesis, angiostasis (Tzouvelekis et al., 2012) and genes involved in the pathogenesis of lung fibrosis (Piotrowski et al., 2014).

Epidemiologic data and the predominance of thoracic involvement suggest that the antigen, which remains unidentified, is inhaled (Müller-Quernheim et al., 2012). Exposure to antigens such as infectious, organic and inorganic agents in genetically susceptible individuals has been proposed (Sinha et al., 2016). Possible etiologic agents include exogenous agents − infectious, environmental, occupational agents, metals, organic and inorganic dusts, mildew, tree pollen, pesticides, insecticides, solvents or silica (Bindoli et al., 2016;

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Iannuzzi et al., 2007). Besides exogenous triggers, also self-compounds, such as serum amyloid A, vimentin, the zinc finger protein 688 and the mitochondrial ribosomal protein have been found to play a possible role in the development of sarcoidosis, acting as autoantigens (Beijer et al., 2017; Bindoli et al., 2016; Häggmark et al., 2015).

Our understanding of the pathophysiology of sarcoidosis is largely derived from studies in acute stage of the disease, wherein cell-mediated responses predominate (Baughman et al., 2011a,b). The oligoclonal expansion of T lymphocytes suggests that sarcoidosis is antigen driven (Müller-Quernheim et al., 2012). After the contact with antigen, resident antigen-presenting cells traffic to regional lymph nodes and present to circulating $CD4^+$ lymphocytes. Those with a T-cell receptor capable of recognizing antigen become activated and proliferate. Via chemokine signalling, these lymphocytes are recruited to the initial site of inflammation and polarized to a Th_1 phenotype and release cytokines, which drive the activation and organization of macrophages (Baughman et al., 2011a,b; Grunewald and Eklund, 2007; Moller, 2003). In conjunction with tumour necrosis factor (TNF)-α signalling, these cell-mediated responses result in the formation of granulomas, the histopathologic hallmark of disease (El-Zammar and Katzenstein, 2007). Granulomatous inflammation occurs primarily along lymphatic tracks, which course along bronchovascular bundles and through interlobular septa (Patterson and Strek, 2013).

2. Clinical manifestations of sarcoidosis

Sarcoidosis has innumerable clinical manifestations, as the disease may affect every organ. Furthermore, the severity of sarcoidosis may range from an asymptomatic state to a life-threatening condition. The lung is the organ most commonly involved with sarcoidosis with at least 90% of sarcoidosis patients. The skin, eye, liver, and peripheral lymph node are the next most commonly clinically involved organs in most series, with the frequency of involvement ranging from 10 to 30% (Judson, 2015).

Sarcoidosis may present as an acute illness, the prototypical acute presentation of sarcoidosis is Lofgren's syndrome, where fever, painful erythema nodosum skin lesions, and/or ankle arthritis quickly develop along with bilateral hilar adenopathy on chest imaging (Prasse et al., 2008). The granulomatous inflammation of sarcoidosis may resolve spontaneously, or due to treatment (Baughman et al., 2011a,b; Chappell et al., 2000). In a minority of cases, sarcoidosis may cause fibrosis of involved organs, that usually determines the prognosis of the disease (Chappell et al., 2000). The symptoms of pulmonary sarcoidosis are nonspecific, including dyspnoea, cough, wheezing, chest pain (Kalkanis and Judson, 2013; McKinzie et al., 2010). Pulmonary fibrosis from sarcoidosis is usually slowly progressive but may be life-threatening because of the development of respiratory failure, pulmonary hypertension, or haemoptysis related to a mycetoma or bronchiectasis. Some manifestations of sarcoidosis (fatigue syndromes) are not organ-specific and probably are the result of a release of mediators from the sarcoid granuloma (Judson, 2015).

2.1. Cough in sarcoidosis

Cough is troublesome symptom of many diseases, especially prevalent in diseases of respiratory tract. It is also often the symptom which makes the patient to seek medical care, because it severely decreases quality of life. The prevalence of cough in patients with sarcoidosis has been estimated to be between 3 and 53%: Japan 3%, Finland 33%, Saudi Arabia 40%, United Kingdom 50% and Turkey 53% (Harrison, 2013).

Objective 24-h cough monitoring proved that patients with sarcoidosis have significantly higher cough frequency when comparing to healthy controls and their cough has diurnal variation pattern (Sinha et al., 2016). It seems to be unevenly distributed across the population − in a large outpatient sarcoidosis cohort, cough was worse in population of African origin than in Caucasians. Cause of the racial difference in cough severity is unclear. The reason could be that sarcoidosis tends to be more severe in black compared to white patients, blacks have been shown to have more organ involvement, higher Scadding stages on chest radiographs, and greater pulmonary dysfunction (Baughman et al., 2001; Judson et al., 2012).

Cough is more prevalent in women sarcoidosis patients compared to men (Harrison, 2013). This phenomenon is in agreement with epidemiological data from specialized cough clinics, which clearly indicate that subjects suffering from chronic cough are predominantly female (Morice et al., 2014). It is known that there are gender differences in the maturation and physiology of the cough reflex, which can contribute to this gender-specific finding (Plevkova et al., 2017). Moreover, women have been found to have higher Scadding stages and more frequent pulmonary symptoms than men in sarcoidosis cohorts (Judson et al., 2017; Ungprasert et al., 2016).

None of the age, spirometric measures, Scadding stage or smoking are relevant predictors of cough severity in sarcoidosis (Judson et al., 2017). The only predictor of objective cough frequency in this cohort is a cough reflex sensitivity measured by capsaicin inhalation test (Sinha et al., 2016). What should be considered is the independence of cough in spirometric measures (Judson et al., 2017; Sinha et al., 2016). FVC has been recommended by an international group of sarcoidosis experts as the favoured objective endpoint, indicating the severity of the diseases (Baughman et al., 2012). In addition, clinicians tend to focus on objective test, including lung functions measurements, to assess the effectiveness of anti-sarcoidosis therapy. However, patients are more concerned with symptoms and quality-of-life issues rather than objective measurements. It suggests that FVC and other spirometric measures are not reliable surrogates for cough in pulmonary sarcoidosis (Baughman et al., 2012).

2.2. Mechanisms of cough in sarcoidosis

Pathogenesis of cough in sarcoidosis is unclear; however, several mechanisms could contribute to cough in this population. In contrast to other chronic lung diseases, such as interstitial pulmonary fibrosis or pulmonary arterial hypertension, there is no widely accepted or implemented animal model for this disease so far (Hu et al., 2017). Since there is insufficient understanding of sarcoidosis, it is difficult to develop appropriate small animal models. Although cats, dogs and horses are reported to very rarely develop similar pathology, there are no tractable, spontaneous models (Altmann and Boyton, 2006). Limitation of current animal models is the lack of chronic granuloma formation, or, respectively, lack of demonstrated chronicity (Hu et al., 2017). Next limitation of current animal models, with respect to cough is that most of sarcoidosis animal models use mice (Chen et al., 2010; Huizar et al., 2011; Kishi et al., 2011; Minami et al., 2003; Nishiwaki et al., 2004; Samokhin et al., 2011, 2010; Swaisgood et al., 2011; Werner et al., 2017). Next model is rat (Herndon et al., 2013). However, mice and rats are not suitable models for cough research, because they do not exhibit a cough reflex that resembles human cough (Belvisi and Bolser, 2002). Most useful animal in research of cough is guinea pig, but attempt to develop guinea pig model of sarcoidosis was unsuccessful (Bowman et al., 1972). Physiology of the cough neural pathways have been recently extensively reviewed based on new results, bringing substantial advances to the understanding of this defensive mechanism (Belvisi et al., 2016; Narula et al., 2014). However, to understand the pathogenesis of cough in sarcoidosis it is necessary to clarify the most relevant information about the cough targets and possible cough triggers.

2.3. Targets and sensors of the cough neural pathways

The targets are the afferent nerves innervating the airways. They are terminals of the vagus nerve with the neuronal bodies located in the nodose and jugular ganglia. Based on their activation profile, airway