

Tiredness, sleep disturbances and pulmonary involvement in patients with primary Sjögren's syndrome

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Tiredness, sleeping habits and quality of life

Patients with rheumatic disorders frequently complain of generalised tiredness or fatigue. Several studies connect this fatigue with the inflammatory activity of the rheumatic disease, e.g. in rheumatoid arthritis. However, several other factors may influence the well-being and the physical capacity of the rheumatic patients, e.g. quality of sleep. Disabling fatigue is one of the most frequent complaints by the patient suffering from primary Sjögren's syndrome, together with the sicca symptoms and pain problems (1,2,3). However, there are few studies that focus on this subject.

Tiredness

Fatigue in patients with Sjögren's syndrome seems to be both more frequent and of higher degree than reported in patients with rheumatoid arthritis or systemic lupus erythematosus (3). The degree of daytime fatigue reported by patients with Sjögren's syndrome is not related to the inflammatory activity as measured by ESR, CRP, Hb or serological findings (2,3). Thus, the fatigue may be a better indicator of the disease activity than the laboratory findings. However, although the inflammatory activity does not correlate with the fatigue, the underlying causes of the fatigue in Sjögren's syndrome may be due to complications, e.g. anemia, hypothyreosis or distal renal tubular acidosis. The fatigue may also be due to involvement of the autonomic nervous system (1). In this context, it is of interest that patients with primary Sjögren's syndrome score high on depression and anxiety scales (see below). Furthermore, there is also a link between Sjögren's syndrome and conditions such as fibromyalgia and chronic fatigue syndrome.

Therapy alternatives are limited, although hydroxychloroquine may be recommended, and recently low-dose hydrocortisone has been reported to be effective in the short term in patients with chronic fatigue syndrome (4).

Sleep disturbances

Clinically, poor sleep is a common complaint in various types of illnesses, especially in pain disorders. Sleeping disturbances in rheumatoid arthritis, osteoarthritis and fibromyalgia are well documented. As patients with Sjögren's syndrome frequently suffer from daytime fatigue as discussed above, we were interested in their sleeping habits. By using a standardised sleep questionnaire and polysomnography we found that patients with primary Sjögren's syndrome suffer significantly from difficulties in both initiating and maintaining sleep, resulting in two hours sleep deficit every night (3). Similar findings have been confirmed by others (5). Not only did pain disturb sleep, but also muscular tension, restless legs and sweating as well as racing thoughts and anxiety. Some patients complained of vegetative and possible neuropsychiatric symptoms during the night. The patients also reported significant daytime problems due to impaired sleep and several patients stated that they did not feel rested after sleep and they also related their fatigue and reduced daily activity to their sleep disturbances.

Cytokines may influence sleep; thus the inflammatory activity of the disease might be a factor of interest. However, we found no correlation between a disturbed sleep pattern and the inflammatory activity as defined by acute phase reactants in our patients. Whether or not an improvement in sleep in patients with primary Sjögren's syndrome reduces these symptoms and in particular fatigue is unknown.

Quality of life

As Sjögren's syndrome is a chronic disorder and there is no curative treatment to offer the patients, it is of clinical importance to have knowledge of the quality of life of patients suffering from Sjögren's syndrome. We have used a standardised questionnaire; Psychological General Well-Being Index (PGWB) to evaluate how patients with Sjögren's syndrome are affected by their disease (6). The PGWB questionnaire evaluates the respondents both generically and psychologically. Our patients with primary Sjögren's syndrome had a significantly lower well being PGWB-index score compared with patients with rheumatoid arthritis. This study also indicated that the group of patients with primary Sjögren's syndrome had a higher score on the subscale of anxiety and depression. Other studies have confirmed a high frequency of anxiety and depression in these patients (1,7) and sleeping problems are also described as discussed above (3).

Thus, these studies indicate that patients with primary Sjögren's syndrome have a high degree of distress and a low sense of well being, which has significant influence on their quality of life.

Pulmonary involvement

In recent years there are an increasing number of studies dealing with pulmonary involvement in patients with primary Sjögren's syndrome. The majority of these studies are uncontrolled cross-sectional studies, while a few studies are prospective or follow-up studies, and a lesser number of studies deal with therapy alternatives addressed against pulmonary manifestations occurring in primary Sjögren's syndrome. Furthermore, several case reports have also been published reporting a wide spectrum of pulmonary manifestations associated with Sjögren's syndrome. In addition, the various sets of diagnostic criteria used in these studies, a different selection of participating patients, the effects of current or past drug therapy and different criteria for definition of pulmonary abnormalities, all give rise to difficulties in the interpretation of data obtained in these studies. In this section a review will be given of the latest studies dealing with pulmonary problems occurring in patients with primary Sjögren's syndrome. This subject has also recently been extensively reviewed by others (8).

Respiratory symptoms

Several studies indicate that the majority of patients with primary Sjögren's syndrome have subjective respiratory symptoms, not only from the upper airways due to dryness of the nasal mucosa resulting in impaired smell, epistaxis and obstruction of the Eustachian tube, but also from the lower respiratory tract. About one third of the patients report a dry non-productive cough or so-called xerothracheitis. Another one third of the patients report exertion dyspnea, intermittent wheezing, chest tightness or breathlessness (9). These respiratory symptoms may partly be caused by airway hyper-reactivity (see below). An increased incidence of bronchitis and lower respiratory tract infections is also reported.

Lung function testing

Studies using spirometric function tests demonstrate that patients with primary Sjögren's syndrome frequently have abnormal test results, even though the patients may be without subjective lung symptoms. Thus, the clinical relevance of these abnormal spirometric findings is uncertain. In our experience 29% have signs of diffuse interstitial lung dysfunction shown by impaired total lung diffusion capacity (TLCO), another 29% have small airway disease shown by diminished V_{E25} without a sign of obstruction in the larger airways and finally 19% of our patients have signs of obstructive lung dysfunction with diminished FEV1 and specific Gaw (9).

Longitudinal studies of pulmonary function in primary Sjögren's syndrome have demonstrated conflicting results. A study by Kelly et al. showed significant reduction in lung function (FEV1, FVC and TLCO) in the course of time (10), while other studies demonstrate unchanged lung

volumes (11,12) and even an increased TLCO, suggesting an improvement in lung status over time (11). According to our experience spirometric findings of an eight-year follow-up in a group of patients with primary Sjögren's syndrome indicate a gradual progression toward restrictive lung function (decreased FRC, VC, FVC and static compliance) (manuscript in preparation).

Sixty per cent of patients with primary Sjögren's syndrome have bronchial hyper-responsiveness (BHR) to inhaled aerosolised methacholine, while only 10% of the control population have mild BHR (9). The BHR in primary Sjögren's syndrome correlated strongly with subjective symptoms of xerotracheitis and all patients with spirometrically small airway disease had BHR, while not all patients who had obstructive lung function had evidence of BHR. In our follow-up study BHR did not change over time and did not lead to obstructive ventilatory function or progression of small airway disease (manuscript in preparation). The mechanism behind BHR in patients with primary Sjögren's syndrome is not known, but it may be mediated by increased osmolarity in the bronchial mucosa secondary to the dryness in the airways or it may be related to bronchial or tracheal inflammation as in asthma. We have also found an increased concentration of nitric oxide in expired air in patients with primary Sjögren's syndrome, similar to that described in asthma (13). On the contrary, patients with primary Sjögren's syndrome have a different pattern of BHR than patients with asthma when comparing three different challenge agents; methacholine, adenosine or cold air (14). In this context, it is also of interest that BHR in primary Sjögren's syndrome, unlike bronchial hyperactivity associated with asthma, does not respond to inhaled corticosteroids or sodium cromoglycate (15), which indicates a different mechanism behind BHR in primary Sjögren's syndrome and bronchial asthma.

Medical imaging

Chest radiography of patients with primary Sjögren's syndrome frequently shows abnormal findings (8-24%), for example minimal diffuse nodular or reticular intensity patterns. These changes may be uni- or bilateral. Pleural thickenings or pleural effusion are rarely described.

It has been demonstrated in several studies that high-resolution computed tomography (HRCT) is informative of pathologic processes in the pulmonary tissue. Salaffi et al. conducted a two-year prospective study to evaluate the role of HRCT in comparison with cells recovered by bronchoalveolar lavage (BAL) as well as lung function studies in a group of patients with primary Sjögren's syndrome (16). They demonstrated, firstly, that the lymphocytic alveolitis may spontaneously regress, and secondly, that there was an association of BAL lymphocytes and neutrophils with abnormal findings on chest HRCT. Thus, HRCT is far more sensitive than chest radiography, and it also appears to be more specific than patient history or spirometric findings in detecting interstitial lung disease in patients with primary Sjögren's syndrome.

Positive Gallium-67 scanning of the lung in primary Sjögren's syndrome has been reported, but the Gallium uptake neither correlates with the clinical findings, abnormalities in lung function tests nor with BAL-findings. Thus, positive Gallium scanning seems to indicate subclinical inflammation in the lung tissue, which is in context with the finding of subclinical alveolitis diagnosed by BAL in patients with primary Sjögren's syndrome (see below).

Bronchoalveolar lavage studies

Bronchoalveolar lavage (BAL) studies have increased our knowledge of the pathogenesis of different lung processes in connective tissue disorders. However, it is still a matter of debate whether the cells recovered by BAL are considered to represent the cell population in the alveolar tissue or the cell population in the larger airways. This is of importance when discussing results of BAL studies in primary Sjögren's syndrome. Furthermore, the clinical significance of asymptomatic alveolitis, diagnosed by an increased number of cells in BAL fluid, is not well documented in view of the prognosis of interstitial lung diseases.

The prevalence of lymphocytic alveolitis is high in patients with primary Sjögren's syndrome (17,18). Almost every second patient has an increased cell count in BAL fluid, often with normal spirometric and chest x-ray findings (17). However, other studies suggest that BAL abnormalities correlate with clinical findings (18). Earlier studies have reported an increased number of activated CD4+ and CD8+ cells in the BAL fluid of patients with primary Sjögren's syndrome (19). We have extensively studied the cellular and cytokine content in BAL fluid of patients with primary Sjögren's syndrome and healthy controls in comparison with patients with systemic sclerosis. We did not find any correlation between cell subsets or cytokine levels with clinical findings or BHR in patients with primary Sjögren's syndrome. Furthermore, the lymphocytic activation was similar in patients and controls; thus the study indicated that lymphocytic activation in the lower respiratory tract reflected immune surveillance, rather than a pathogenetic process (19).

Bronchial and lung biopsies

Biopsy studies of the bronchial mucosa of patients with primary Sjögren's syndrome report that 20-31% of the patients have atrophy and flecking of the bronchial lining epithelium and follicular lymphocytic infiltration of the mucosa, mainly in exocrine mucous glands of the small airways (20). Immunohistochemical studies of the airways of patients with Sjögren's syndrome also demonstrate a dense lymphocyte infiltration of CD3+ and CD4+ cells. We have also found an increased number of IL-8 positive cells, while patients with asthma present IL-4 and IL-5 positive cells (21).

In studies on transbronchial biopsies in primary Sjögren's syndrome a spectrum of histological changes, both lymphocytic infiltration in the interstitium as well as in the peribronchial space, has been reported (8,21). These studies demonstrate that pulmonary fibrosis also exists in primary Sjögren's syndrome, although lung fibrosis is not as common as in other connective tissue diseases, e.g. systemic sclerosis. In a study by Gardiner the frequency of interstitial fibrosis in primary Sjögren's syndrome was 8% (22). A few cases where bronchiolitis obliterans organising pneumonia (BOOP) was associated with Sjögren's syndrome have also been reported. In some of their cases high-dose corticosteroid therapy has been successful. Other papers report an association between pulmonary hypertension and Sjögren's syndrome, and pulmonary amyloidosis has also been reported in a patient with primary Sjögren's syndrome.

Deheinzeln et al. treated 11 patients with signs of interstitial lung disease due to primary Sjögren's syndrome for 6 months with azathioprine and glucocorticoids. Patients on an active regimen improved significantly in forced vital capacity compared to untreated patients (23). Others have reported cases where treatment with intravenous pulse cyclophosphamide (24) and low-dose cyclosporin has been effective and well tolerated by patients with pulmonary complication due to primary Sjögren's syndrome.

The relative risk of lymphoma in Sjögren's syndrome is 44. In a study of 50 patients with Sjögren's syndrome and lymphoma, ten patients had their lymphoma in the lung (25). The histopathological findings of lymphoma reported in Sjögren's syndrome have a wide spectrum, from benign pseudolymphoma proliferation to B-cell non-Hodgkin's lymphoma, both high and low grade lymphomas. These lymphoma tumours are treated by standard chemotherapy regimens and/or radiation therapy and they respond to therapy similarly as other forms of lymphoma.

Summary

Patients with primary Sjögren's syndrome often have subjective symptoms from the upper and lower respiratory tracts and frequently seem to have subclinical pulmonary involvement evaluated by lung function tests, HRCT or BAL studies. The long-term prognosis of these manifestations is uncertain. However, there are some cases of patients with primary Sjögren's syndrome who may demonstrate life threatening pulmonary complications due to the disease.

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