Progress in the pathogenesis and treatment of rheumatoid arthritis with sleep apnea hypopnea syndrome

Jian-Wei Xiao, Xu Cai, Fen-Lian Guo, Yi-Wei Hong, Zhi-Hua Yin, Xin-Peng Chen, Li-Ping Dai, Zhi-Zhong Ye

Department of Rheumatology, Shenzhen Futian Hospital for Rheumatic Diseases, Shenzhen, Guangdong Province, 518000, China

ARTICLE INFO

Objective: Sleep apnea hypopnea syndrome (SAHS) is a common sleep disorder, which is manifested as a reduction in tidal volume or apnea during sleep, which results in intermittent hypoxia and tissue hypoxia and induces oxidative stress and inflammatory responses. Rheumatoid arthritis (RA) is a systemic disease contributing to hyperplasia of synovial membrane, cartilage erosion and joint damage. Fibroblast like synoviocytes (FLS), which make up the lining of the synovial membrane, are believed to play a role in the pathogenesis of RA. RA is a series of inflammation-like responses that induce joint damage and dysfunction and impair patients’ life quality. This article first introduced the basic features of RA and analyzes the pathogenesis of RA with SAHS. Then the relationship between RA and SAHS was investigated. Finally, the progress in the treatment for RA with SAHS was reviewed emphatically.

ABSTRACT

1. Introduction

Sleep apnea hypopnea syndrome (SAHS) is a systemic disease rather than a simple sleep disorder. Patients with SAHS usually suffer from daytime drowsiness and repeated apnea during sleep, which has an adverse impact on patients’ life quality and safety[1]. Rheumatoid arthritis (RA) is a systemic disease which causes hyperplasia of synovial membrane, cartilage erosion and joint damage. Synovial membrane is usually the first affected site of RA, presenting as hyperplasia and inflammatory responses of the synovial membrane and causing damage to cartilages and bones. However, the pathogenesis of RA is still not fully clarified.

Inflammatory responses are the shared features of both RA and SAHS. Sleep apnea may aggravate inflammatory responses, which in turn cause deterioration of RA. If the symptoms of SAHS cannot be redressed, it will cause multi-system and multi-organ damage.

Aggravation of RA is precisely induced by the intense inflammatory response associated with SAHS. Once the symptoms of SAHS are eased, the clinical symptoms of RA will also be improved. The present study attempts to reveal the relationship between the two conditions and review the latest progress in treatment. We hope our research findings can help relieve the clinical symptoms and improve the life quality of patients.

2. Features of RA

The lining of synovial membrane is made up of two to three layers of macrophage-like synovial cells and fibroblast like synoviocytes (FLS) as the inner layer with dense matrix. Antigen production is regulated by the macrophage-like synovial cells, FLS, activated lymphocytes and dendritic cells. RA is considered as an abnormal immune response of the host. Due to antigen action, the immune response promotes the maturation of B lymphocytes. After maturation, B lymphocytes will secrete high-affinity antibodies. Although it has not been confirmed which antibody causes RA, it
is generally recognized that different endogenous and exogenous antigens play a role in disease development to varying extent. Components released by the damaged joint tissues and apoptotic cells and not yet accommodated by the immune system are the autoantigens to which the specific antibodies bind. An increase in antigen-antibody complexes will activate the inflammatory signals and aggravate inflammation. Although the manifestations of RA vary from one patient to another, most patients have lymphocyte infiltration to varying extent[2]. Lymphocytes usually make disordered invasion, including activated T-cells and B-cells around FLS and macrophage-like synovial cells with irregular distribution. Lymphocyte invasion will further aggravate FLS proliferation and inflammation, forming cystic germinal centers in the synovial membrane. About 20% of the RA patients are associated with invading lymphocytes from the blood. What cause bone destruction and bone resorption are the cytokines, chemokines, matrix metalloproteases (MMPs) and angiogenic factors released by the altered synovial membrane. Bone invasion and chronic inflammation of the synovial membrane, regulated by the activated FLS, play a key role in the pathogenesis of RA[3]. FLS has proliferative properties of the stem cells, and the compensational regeneration of FLS is usually derived from joint damage. Some FLS may be mesenchymal cells and matrix cells from blood circulation or may be derived from bone marrow from vessels. Proliferating FLS will release tumor factors and chemokines, such as interleukin-6 (IL-6), interleukin-8 (IL-8) tumor necrosis factor (TNF-α), interleukin-15 (IL-15) and stromal cell derived factor-1 (SDF-1). Lymphocytes migrate from the blood vessels to the synovial membrane, and after activation, they will be promoted by inflammatory factors[4]. Extracellular matrix proteins are synthesized by FLS, such as cell adhesion factors and fibronectin, which promote lymphocyte recruitment and retention. Furthermore, FLS promotes differentiation of B lymphocytes. MMP3 and matrix-degrading enzymes are the factors promoting cartilage degradation. FLS can enhance the immune response against antigens derived from cartilage degradation and promote SDF-1 and other vascular endothelial growth factors (VEGFs). FLS also has a promoting effect on fibroblast growth factor (FGF)- and platelet-derived growth factor (PDGF)-mediated angiogenesis[5]. NF-kB ligands expressed on FLA and T-cells interact with the uniceptor RANK expressed on the monocytes, thus promoting osteoclast differentiation and bone resorption and regulating the formation of cartilage-damaging pannus. This will cause irreversible damage[6]. In a word, RA is a series of inflammatory responses, which aggravate the damage, cause dysfunction in patients and affect patients’ daily life. Therefore, controlling inflammatory responses is crucial for the treatment of RA. However, SAHS will definitely exacerbates the inflammatory response in RA patients, accelerating progression of RA.

3. Pathogenesis of RA with SAHS

Many factors may lead to SAHS, which causes hypoxemia through sleep apnea or hypoventilation. The patients will have hypoxic stress responses, which aggravate inflammatory responses and RA, or even lead to multiple organ failure, asphyxia and death in sleep[7]. Repeated apnea may cause pulmonary and systemic hypertension, leading to arrhythmia, heart failure, chronic cerebral hypoxia and kidney insufficiency. The present study divides SAHS into central and obstructive type based on pathogenesis.

3.1 Central type

The control of the respiratory system by the advanced nervous system such as brainstem and medulla oblongata is weakened during sleep. Accordingly, the emergency responsiveness of the body to hypoxemia is also lowered. That is why lesions of the respiratory muscles can lead to sleep apnea.

3.2 Obstructive type

Obstructive sleep apnea (OSA) is the most common type of sleep apnea, with the lesions mainly at the throat and absence of support from intact bony structure in the pharyngeal cavity-postnasal-epiglottis. The size if the pharyngeal cavity is mainly regulated by muscular contraction of the pharyngeal cavity. Muscle tone usually reduces around the pharyngeal cavity in sleep. Moreover, a supine position is usually taken in sleep, and this gesture will cause the posterior displacement of tongue root and soft palate under gravity pull, leading to narrowing of the pharyngeal cavity. Other causes of pharyngeal stenosis include epiglottic edema, tonsillar hypertrophy and soft palate hypertrophy.

4. Relationship between RA and SAHS

Recent years have witnessed major achievements in the research on SAHS. The major reason for the aggravation of RA due to SAAS is the increase in inflammatory factors caused by hypoxia and sleep disorder, which further leads to aggravation of chronic inflammatory responses[8]. Long-term inflammatory responses will exacerbate the inflammatory response of the synovial membrane, and hence the clinical symptoms of RA. Apparently, improving sleep quality and reducing the levels of inflammatory factors can help ease the clinical symptoms of RA and improve the patients’ life quality[9]. The activated macrophages will produce TNF-α, which directly or indirectly stimulates the secretion of inflammatory factors by the inflammatory cells. TNF-α is the major inflammatory factor involved in inflammatory responses[10]. IL-6 is a pro-inflammatory factors and chemokines, such as interleukin-6 (IL-6), interleukin-8 (IL-8) tumor necrosis factor (TNF-α), interleukin-15 (IL-15) and stromal cell derived factor-1 (SDF-1). Lymphocytes migrate from the blood vessels to the synovial membrane, and after activation, they will be promoted by inflammatory factors[4]. Extracellular matrix proteins are synthesized by FLS, such as cell adhesion factors and fibronectin, which promote lymphocyte recruitment and retention. Furthermore, FLS promotes differentiation of B lymphocytes. MMP3 and matrix-degrading enzymes are the factors promoting cartilage degradation. FLS can enhance the immune response against antigens derived from cartilage degradation and promote SDF-1 and other vascular endothelial growth factors (VEGFs). FLS also has a promoting effect on fibroblast growth factor (FGF)- and platelet-derived growth factor (PDGF)-mediated angiogenesis[5]. NF-kB ligands expressed on FLA and T-cells interact with the uniceptor RANK expressed on the monocytes, thus promoting osteoclast differentiation and bone resorption and regulating the formation of cartilage-damaging pannus. This will cause irreversible damage[6]. In a word, RA is a series of inflammatory responses, which aggravate the damage, cause dysfunction in patients and affect patients’ daily life. Therefore, controlling inflammatory responses is crucial for the treatment of RA. However, SAHS will definitely exacerbates the inflammatory response in RA patients, accelerating progression of RA.
mediator secreted by monocytes and T-lymphocytes. Its roles include inducing the differentiation and proliferation of T-lymphocytes and antibody release from B lymphocytes. As a result, the neutrophils will accumulate and be activated, which further promotes the liver secretion of acute phase reaction protein, which is involved in the activation of acute and chronic inflammatory responses. Such secretion will be further enhanced by temporary hypoxia, which in turn aggravates overall inflammatory responses as well as inflammatory responses of the synovial membrane. This is considered as the mechanism of aggravating clinical symptoms in RA patients. In a word, inflammatory responses are the primary reason for impairment of life quality in RA patients[11]. See Fig. 1.

5. Progress in the treatment for RA with SAHS

5.1 Continuous positive airway pressure therapy

Continuous positive airway pressure therapy (CPAP) is the most commonly used treatment for SAHS. It has been demonstrated at home and abroad that CPAP not only improves sleep apnea, but also alleviates the tissue damage caused by sleep apnea, thus improving the prognosis[12]. The treatment mechanism is presumed as follows (Fig. 2)[12]: (1) CPAP can reduce the probability of cerebrovascular complications and improve metabolic abnormalities. In one study, the patients were randomly divided into two groups, which received CPAP and virtual CPAP, respectively. The metabolic indicators were compared between the two groups 3 months later. It was found that CPAP significantly relieved metabolic abnormalities in patients[13]; (2) CPAP reduces the severity of oxidative stress responses and inflammatory responses in SAHS patients. In another study, severe SAHS patients received CPAP and polysomnography (PSG) monitoring during the entire process. The changes in inflammatory markers in the serum and condensate of exhaled air were detected. The main inflammatory markers detected were TNF-α, IL-6, peroxynitrite, and 8-isoprostane. After treatment for a period, PSG results were greatly improved, and the levels of peroxynitrite and 8-isoprostane in the serum and condensate of exhaled air decreased dramatically. This indicated that CPAP not only reduced the airflow inflammatory response and stress response in SAHS patients, but also controlled the systemic stress response and inflammatory response[14]; (3) SAHS is very likely to cause atherosclerosis and cardiovascular diseases, thus further leading to endothelial dysfunction[15]. CPAP can improve endothelium-dependent vasodilation, reduce cardiovascular and cerebrovascular complications and increase cerebral blood flow, thereby finally improving the neural function of SAHS patients[16].

5.2 Medication therapy

Recently, some scholars have experimented with medication therapy in SAS. In one study, SAHS patients were randomly divided into two groups. One group received acetazolamide treatment. The results showed that acetazolamide improved the sleep quality of the patients to a certain extent, redressing respiratory disturbance and improving oxygenation[17-19]. Sulfanilyl radical in zonisamide inhibits carbonic anhydrase and improves respiratory disorder in sleep, thereby reducing the probability of sleep apnea[20-22]. However, medication therapy does not exhibit any advantages of CPAP. Intermittent hypoxia caused by apnea is the core factor aggravating oxidative stress responses and inflammatory responses. In theory, anti-oxidative treatment may have a salient efficacy[23,24]. But the researches on anti-oxidative treatment for sleep apnea are still at the stage of animal experiments. It has been shown that N-acetylcysteine (NAC) and melatonin (MEL) have a protective effect against liver damage and cell apoptosis. NAC has history of clinical use for dozens of years. NAC can be used as the precursor for glutathione...
synthesis and increases the intracellular level of glutathione, thereby exerting an anti-oxidative effect\textsuperscript{25,26}. NAC has proven safe after many years of clinical use, with good anti-inflammatory and anti-oxidative effects. NAC is recommended for SAHS patients intolerant to CPAP\textsuperscript{27–30}.

To conclude, our understanding about SAHS is insufficient and should be enhanced through clinical practice, so as to provide more reasonable treatment for the patients. The pathogenesis of SAHS is a slow process and is not fully known yet. But one thing is for sure, that is, SAHS can produce severe damage to the body and tissues, thus aggravating inflammatory responses. For RA patients, this response mechanism only makes the situation worse. The inflammatory response can be relieved by improving SAS, which is also conducive to relieving the clinical symptoms of RA. However, our study had certain limitations. Firstly, the sample size was small, and it remains to fully clarify the influence of SAHS on the patients and to boost clinical treatment.

References

\begin{enumerate}
\item Huang JS, Wang T. Progress in the treatment for central sleep apnea. \textit{Chin J Neurol 2017; 50(1): 74-78.}
\item Almendros I, Khalyfa A, Trzepizur W. Tumor cell malignant properties are enhanced by circulating exosomes in sleep apnea. \textit{Chest} 2016; 150(5): 1030-1041.
\item Gao J, Li YJ. Research progress in pathogenesis and traditional Chinese medicine as targeted therapy for rheumatoid arthritis. \textit{Chin Pharm} 2016; 27(35): 5030-5034.
\item Gupta MA, Jarosz P. Obstructive sleep apnea severity is directly related to suicidal ideation in posttraumatic stress disorder. \textit{J Clin Sleep Med} 2018; 14(3): 427-435.
\item Snyder B, Cunningham RL. Sex differences in sleep apnea and comorbid neurodegenerative diseases. \textit{Steroids} 2018; 5(133): 28-33.
\item Tang Y, Gao XL, Li JQ. Progress research on serologic markers related to OSAHS. \textit{Chin Med J} 2017; 97(12): 954-957.
\item Naismith SL, Mowszowski L. Sleep disturbance in mild cognitive impairment: A systematic review of recent findings. \textit{Carr Open Psychiatry} 2018; 31(2): 153-159.
\end{enumerate}