Review

Research progress on the pathogenesis and quality of life of patients with primary Sjögren's syndrome complicated by depression

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ABSTRACT

In the past decade, an increasing number of studies have found a relationship between the occurrence and development of depression and autoimmune diseases, and the high prevalence of depression in patients with connective tissue diseases has also been confirmed. Primary Sjögren's syndrome (pSS) is a chronic autoimmune exocrinopathy characterised by lymphocytic infiltration and exocrine gland destruction. Depression in pSS patients is common, and the factors contributing to this condition are complicated. pSS patients with depression generally have a lower quality of life than pSS patients without depression. Several pathophysiological mechanisms involved in the condition have been proposed in recent years. Thus, in this review, we summarised recent progress on the impact of depression on pSS patients' quality of life, the possible pathogenesis underlying the development of depression in pSS patients and the management of such patients.

Introduction

Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest, which can influence people's daily work, relationships and health conditions, resulting in lower quality of life (QoL) and productivity (1). Concomitant depression in patients with chronic diseases is very common, and these chronic conditions generally include cardiovascular disease, arthritis, diabetes, cancer and so on.

Recently, increasing attention has been given to the high prevalence of depression in patients with connective tissue diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) (2), since this mood disorder could seriously affect patients' treatment outcomes. At the same time, the relationship between the occurrence of depression and the immunoinflammatory background associated with connective tissue diseases has been increasingly recognised by researchers (3, 4).

Primary Sjögren's syndrome (pSS) is a chronic autoimmune exocrinopathy characterised by lymphocytic infiltration and exocrine gland destruction, and the disease can also have extraglandular features such as pain, fatigue, depression and anxiety. Depression is common in pSS patients, with a high prevalence of 32–45.8% (5), which can have a profound negative impact on patients' QoL and compliance.

Several causes, including symptoms of pSS, psychological factors and social environmental factors, may lead to depressive disorders in pSS patients. However, the exact mechanisms of depression in pSS patients remain unclear. In the past decade, many researchers have carried out studies to answer this question. The findings have demonstrated that structural changes in the brain, dysfunction of the cytokine regulatory network and elevated activation of the autoimmune inflammatory system can co-contribute to the development of depression in the context of immune inflammation in pSS.

Thus, in this review, we summarise recent findings examining the impact of depression on pSS patients' QoL and mainly discuss the possible pathogenesis underlying the development of depression in pSS patients and the management of such patients.

pSS comorbid with depression causes impaired health-related quality of life

Increasing evidence has demonstrated that patients with pSS have a higher

risk of developing anxiety and depression than normal controls (6-8). Liu *et al*. also found that pSS patients had higher scores on the Hospital Anxiety Scale (HAS) and Hospital Depression Scale (HDS) [7 (4, 10) and 6 (3, 10), respectively] than patients with other internal diseases (3.37±2.81 and 3.83±3.14; both $p<0.001$) (9), suggesting that pSS patients may suffer more from mood disorders.

QoL is the degree of the general well-being of an individual based on the social background and the individual's goals, expectations and concerns. Health-related quality of life (HR-QoL) includes physical and mental health perceptions and other correlates about health, including health risks, functional status and social status. The most commonly used HR-QoL assessment scales include the Short-Form 36 (SF-36), World Health Organization Quality of Life Assessment-Bref (WHOQOL-Bref) and EuroQOL-5 Dimension (EQ-5D), which measure several dimensions, including physical functioning, role limitations, fatigue, emotional well-being, social functioning, pain, general health and so on. The lower the scores are, the worse the QoL. By using these scales, several studies have indicated that depression and anxiety are correlated with impaired HR-QoL (10-13) and that mood disorders could affect patients' HR-QoL in several aspects.

Both Hackett *et al*. and Ng *et al*. pointed out that reduced physical activity in pSS patients was associated with symptoms of depression. These physical activities usually included the most routine activities, such as dressing, eating and walking, which may directly affect HR-QoL (14, 15). Fatigue appears to be most strongly associated with mood disorders in patients, as several studies have demonstrated that depression is a strong predictor of mental and physical fatigue in patients (16-20). Fibromyalgia (FM) is a disorder characterised by widespread musculoskeletal pain accompanied by psychological symptoms and is relatively prevalent in pSS patients (21). Studies have found that the prevalence of FM is higher in pSS patients with more severe depression; in addition, negative mood and emotional dysregulation could aggravate pain severity and disability in pSS patients with FM (22, 23). Depression is also associated with the development of central nervous system (CNS) symptoms in pSS patients. Segal *et al*. concluded that depression partially accounted for cognitive symptoms (24), Tjensvoll *et al*. reported that depressive mood significantly influenced the severity of headache (25), while Li *et al*. found that body image disturbance questionnaire (BIDQ) scores could be predicted by severity anxiety. In addition, just as sleep disturbance is associated with RA and other autoimmune diseases (26), sleep quality is also negatively affected in pSS patients with depression. Priori *et al*. and Cui *et al*. both found that pSS patients, especially those who are in a negative mood, are prone to sleep disturbance, mainly demonstrated by reduced sleep efficiency, an increased number of awakenings and daytime dysfunction (27, 28). Impaired quality of sexual life in female pSS patients with depression is also of concern (29-32); since it is not easy for pSS patients to access medical advice on this issue, sexual dysfunction might also be a factor contributing to depression. Regarding the patient's normal working status, patients with pessimism tended to have a high risk of working disability and not being gainfully employed (33). All of these aspects influenced by mood disorders may subsequently lead to more severe depression and anxiety. In conclusion, pSS complicated with depression can seriously affect patients' HR-QoL.

Factors that contribute to depression in patients with pSS

Several factors, including symptoms of pSS, such as sicca symptoms, fatigue, nervous system symptoms; psychological factors, such as personality characteristics of neuroticism and low sociability; and negative social environmental factors, may co-contribute to depression in pSS patients (Fig. 1).

Sicca symptoms and fatigue could be very common in pSS patients. Sicca symptoms usually include dry eyes, dry mouth, dry skin, vaginal dryness and even persistent dry cough. Several studies have found that symptoms of dry eye and dry mouth rather than pSS itself were correlated with a high risk of depression and anxiety (34-37). Gandia *et al*. also indicated that the severity of dry mouth was significantly correlated with anxiety and depression by using the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) questionnaire to evaluate patients' symptoms ($p=0.004$ and 0.024, respectively) (38). Regarding symptoms of fatigue, which is defined as physical and/or mental exhaustion, both Priori *et al*. and Stack *et al*. reported that patients with pSS complaining about fatigue were more likely to feel depressed (39, 40). Moreover, Segal *et al*. designed a short, self-report scale to measure cognitive symptoms, which refer to a decline in memory and attention, in patients with rheumatic disease, and they found that higher scores for cognitive symptoms in pSS patients were associated with more severe depression (41). In another study conducted by Cavaco *et al*., however, they failed to find a significant association between cognitive impairment and mood disorders, but they suggested that poor performance on auditory verbal learning tests was associated with anxiety ($p=0.024$) and abnormal magnetic resonance imaging (MRI) findings ($p=0.038$) (42). In addition, Mandl *et al*. conducted a follow-up study in pSS patients and indicated that autonomic dysfunction symptoms might lead to anxiety and depression ($r=0.51$ and 0.63; $p=0.01$ and <0.001, respectively) (43). These symptoms mainly include orthostatic intolerance, secretomotor dysfunction, urinary dysfunction, gastrointestinal dysfunction, pupillomotor dysfunction, vasomotor dysfunction, reflex syncope and so on.

Psychological factors play an important role in the development of depression and anxiety. In a study including 40 pSS patients, 56 patients with SLE and 80 healthy participants matched for age and sex, Hyphantis *et al*. indicated that patients with pSS suffered more from general psychological distress than SLE and healthy participants; in addition, less use of humour ($p<0.001$), higher rates of delusional guilt ($p=0.032$) and more use of schizoid fantasy ($p=0.005$)

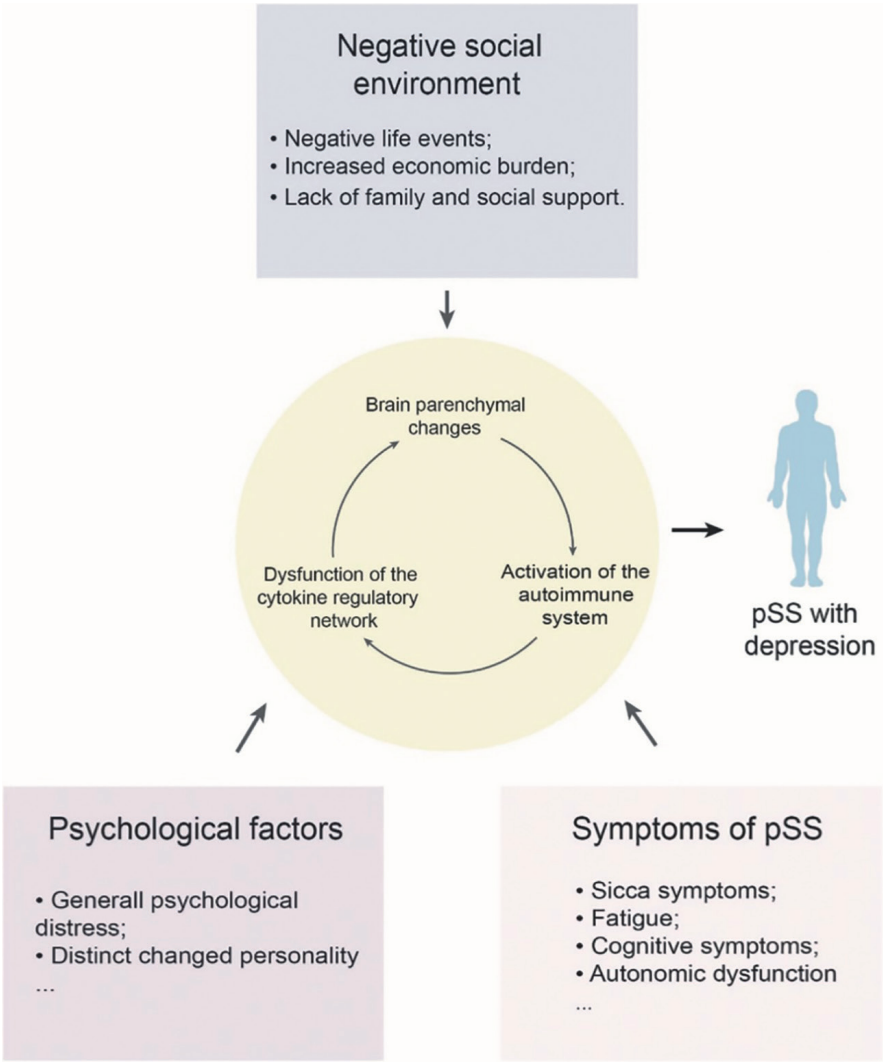

Fig. 1. Aetiology of pSS with depression.
Multiple factors, including the external social environment, psychological factors, symptoms of pSS and internal inflammation and immune disorders, co-contribute to the development of pSS with depression. pSS: primary Sjögren's syndrome.

were also significantly associated with impaired HR-QoL (44). Karaiskos *et al*. and Milic *et al*. both pointed out that compared with healthy participants, pSS patients showed distinct personality characteristics of neuroticism and low sociability (45, 46). These findings suggested that pSS patients were prone to personality changes and that they might focus too much on the disease or access incorrect medical information through informal channels, which could result in a higher tendency to develop depression, anxiety and other psychological disorders.

Negative social environmental factors also contribute to the development of psychological disorders in pSS patients. Compared with pSS patients without depression, Yang *et al*. and Shelomkova *et al*. found that pSS patients with depression experienced more negative life events (24.36±11.24 *vs*. 15.88±9.97, $p<0.05$), including aspects about family, study and work (47, 48). On the other hand, the increased financial burden of treating the disease and the lack of family and social support also contribute to anxiety and depression.

Potential pathogenesis of pSS comorbid with depression

Brain parenchymal structural changes

Increasing evidence has indicated that brain parenchymal structural changes are the basis of neuropsychological problems in patients with SS. A few studies have found an increased frequency of central nervous system white matter lesions (WMLs) in patients with pSS (49, 50). There is also growing evidence linking WMLs to depression (51), so the increased brain WMLs in pSS patients may be partially responsible for developing depression. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a newly discovered but rare autoimmune encephalitis in which psychiatric symptoms might be the only presentation (52). In view of this, if an autoimmune disease patient has begun to develop depression, anxiety or other psychiatric symptoms, anti-NMDAR encephalitis should be considered as one of the differential diagnoses. Additionally, antibodies against the NR1 or NR2 subunits of the NMDA receptor, which are associated with anti-NMDAR encephalitis, might also be involved in the development of mood disorders in autoimmune diseases, including pSS. Xia *et al*. reported a rare case with a long history of major depressive disorder that was finally diagnosed with anti-NMDAR encephalitis by finding anti-NR1 IgG autoantibodies in cerebrospinal fluid, suggesting possible involvement of anti-NR1 antibodies in depressive disorder (53). In addition, Lauvsnes *et al*. conducted a study aimed at finding a connection between the presence of anti-NR2 antibodies and hippocampal atrophy in human diseases and suggested that pSS patients of whom anti-NR2 antibodies were positive in cerebrospinal fluid had less hippocampal grey matter than patients without these antibodies, as had been previously demonstrated in animal models (54-57). This finding suggested that anti-NR2 antibodies may cause neuronal death manifested as reduced hippocampal grey matter and even other structures in the brain, resulting in cognitive impairment and mood disorder. Another study on microstructural changes in the brain in pSS found that patients with pSS, especially those with comorbid depression, may present decreased functional connectivity in the somatosensory cortex and microstructural changes in the corticospinal tracts and major white matter tracts (58).

Immunologically mediated small vascular lesions in the brain have also been

discovered in recent studies. These small and microvascular lesions usually demonstrate lymphocytic inflammation and ischaemic vasculopathy, leading to hypoperfusion and functional impairment in parts of the brain (59-61). Hypotheses regarding depression have suggested that the frontal lobe, temporal lobe, thalamus and other regions are depression-related neural circuits (62) and that damage to neurons and nerve fibers in these regions could cause the development of depression.

Dysfunction of the cytokine regulatory network

It is widely known that the balance between pro- and anti-inflammatory cytokines regulates the magnitude and duration of an immune response to inflammatory stimulation. Once this balance is broken, *i.e.* the secretion of proinflammatory cytokines has increased and/or the synthesis of anti-inflammatory cytokines has been suppressed, a range of pathological inflammation would be present. Cytokines that act on brain signalling pathways could contribute to depressive and anxious symptoms, since recent studies have indicated the association between inflammation and mood disorders (63, 64).

It has been clarified that proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-12, tumour necrosis factor (TNF)-α, and interferon (INF) play important roles in the initiation and progression of pSS, while anti-inflammatory cytokines such as IL-4 and IL-10 confer protective effects during pathogenesis. Most of these cytokines are also involved in depression, among which the roles of IL-1 and IL-6 in the development of depression in autoimmune disease patients have been widely studied (65, 66). IL-1β in the brain, originating from either the periphery or activated microglia, can bind specific receptors on neurons and further induce sickness behaviour, including mood disorders (67). Since Bardsen *et al*. recently found that IL-1β and its related molecules in cerebrospinal fluid (CSF) are associated with fatigue in pSS patients (68), these cytokines may also contribute to depression. Regarding IL-6, Hirohata *et al*. found elevated levels of serum IL-6 and CSF IL-6 in neuropsychiatric SLE (NPSLE) patients, which could manifest as an acute confusional state, anxiety disorder and mood disorder (69), indicating that IL-6 might also play a similar role in the pathogenesis of depression in pSS patients. In addition, some pSS patients, especially those with early onset, might develop SLE over the course of the disease (70); therefore, depression and other psychiatric symptoms mediated by the IL-6 mechanism might partially account for SS/SLE overlap in some cases.

There are three main mechanisms by which cytokines act in the development of mood disorders. First, overexpression of proinflammatory cytokines could affect the vascular endothelium and lead to vasoconstriction, which results in hypoperfusion of WM and dysfunction in emotion-related neurons.

Second, proinflammatory cytokines can cause neuroendocrine disorders, and the hypothalamic-pituitary-adrenal (HPA) axis is an important part of the neuroendocrine system, which is involved in controlling the response to stress and regulating many physical activities, including psychology and immunity. Proinflammatory cytokines may interfere with neuroendocrine functions to cause or aggravate anxiety and depression by activating the HPA axis, dysregulating its receptors, and inhibiting the negative feedback of this axis. On the other hand, evidence suggests that abnormal HPA axis function may lead to uncontrolled secretion of proinflammatory cytokines such as IL-1 and IL-6, thus leading to or exacerbating immune system disorders (71).

Third, cytokines also alter neurobiochemistry. Indoleamine 2,3 dioxygenase (IDO) activated by proinflammatory cytokines reduced serotonin (5-HT) synthesis and increased consumption, leading to the failure of 5-HT1A receptors to exert their anti-anxiety and antidepressant effects (72). On the other hand, a study suggested that IL-1- and TNF-α- induced P38 mitogen-activated protein kinase (MAPK) increased the expression and function of the 5-HT reuptake pump, resulting in decreased synaptic utilisation of 5-HT and depressive behaviour in experimental animals (73). Moreover, it was found that cytokines were involved in interfering with the metabolism of tetrahydrobiopterin (BH4) and phenylalanine, which is also involved in the development of depressive symptoms (72, 74).

Elevated activation of the autoimmune inflammatory system

In the context of chronic immunological inflammation, multiple inflammatory pathways are activated. First, the production of multiple autoantibodies is involved in central nervous system involvement and the development of mood disorders. Apart from the anti-NR1 and anti-NR2 antibodies mentioned above, Karaiskos *et al*. reported that the levels of autoantibodies against alpha-melanocyte-stimulating hormone (α-MSH) in pSS patients were significantly correlated with anxiety scores. Similar results were found in autoantibodies against oxytocin and vasopressin (46), and all of these neuropeptides were stress related. In addition, autoantibodies against myelin (anti-aquaporin-4 antibodies), anti-thyroglobulin antibodies (TGAb) and thyroid peroxidase antibodies (TPOAb) were found to be related to depressive symptoms (58, 75). Second, inflammasomes such as pyrin domain-containing protein 3 (NLRP3), which is highly activated by chronic mild stress, and increasing surface expression of P2X7R on peripheral blood mononuclear cells in patients with pSS, were significantly correlated with the release of IL-1β (76-80) (Fig. 1).

Management of pSS patients with depression

Aiming at the mechanism of depression associated with pSS, some drugs have been applied in the treatment of pSS patients comorbid with depression. Although recent clinical trials have found that using anti-inflammatory drugs, including IL-1 receptor antagonists and rituximab, which is an anti-CD20 monoclonal antibody, to treat pSS patients can improve depressive disorder and mental fatigue (81, 82), some studies have concluded that the improvement is limited (83, 84). Given the current controversy, it is plausible to treat these pa-

tients with anti-anxiety and antidepressant medications, such as paroxetine, in addition to conventional medications for SS.

Exercise therapy can stimulate the pituitary gland to release endorphins, stimulate the nervous system to produce microelectrical stimulation, and relieve muscle tension and depression, which in turn causes the cerebral cortex to relax. Two studies of exercise therapy in the form of a walking program have both demonstrated that the therapy can effectively relieve fatigue and depressive symptoms in pSS patients (85, 86).

Moreover, psychotherapy is also important for patients. In a study comparing illness perceptions and psychological distress in patients with pSS, SLE and RA, Kotsis *et al*. found that, compared with other groups of patients, those with pSS showed little understanding of their disease and attributed more symptoms to their illness (87). Low levels of perception mean that patients may be more worried about the consequences of the disease than patients with other rheumatic diseases, thus leading to a negative attitude toward the treatment, anxious and depressive moods and reduced QoL. Therefore, psychoeducational therapies, behavioural interventions and lectures that are specifically targeted at pSS treatment can improve patients' understanding about the disease and medication, and alleviate patients' negative emotions, contributing to improvements in their HR-QoL.

Recent studies have also demonstrated the efficacy of traditional Chinese medicine (TCM) in improving anxiety/depressive symptoms and HR-QoL in patients with pSS (88-91). This provides a new direction for relieving patients' anxiety and depression by means of integrated Chinese and Western medicine in the future.

Conclusions

Based on the literature in the last decade, it can be concluded that the prevalence of depressive disorder is relatively high among patients with pSS. Mood disorders can affect the QoL of patients in many ways, which hinders the effectiveness of treatment and management of the disease itself. Moreover, the persistence of depression may further aggravate the occurrence and development of autoimmune diseases (92). Therefore, rheumatologists need to pay enough attention to assessments of patients' psychological state when attending them (93).

Factors contributing to the development of mood disorders in pSS patients are complicated, and current evidence suggests that symptoms of pSS, patients' psychological distress and personality changes, and lack of other social support jointly promote the development of anxiety and depression. Regarding pathophysiological mechanisms, the research results in pSS patients are limited. Although brain parenchymal structural changes in pSS patients with depression have been reported and analysed in a few studies, neuroimaging studies, including functional magnetic resonance imaging (MRI) and positron emission tomography (PET) scans, and measures of network connectivity in pSS patients should be conducted further and shed light on the effects of pSS on brain function and its relationship with depression in the future.

The underlying molecular mechanisms remain unclear. Although several specific autoantibodies and pathogenic cytokines, such as anti-NMDAR antibodies, anti-aquaporin-4 antibodies, and IL-1β, have been proposed, these studies examined only a small part of the regulatory network of inflammatory molecules. In addition, most of these findings are derived directly from the results of laboratory examinations of clinical patient specimens. Functional experiments, including *in vivo* and *in vitro* experiments, are needed to further explore the role of these autoantibodies and cytokines in pathogenesis and outline the specific inflammatory pathways involved in the molecular regulatory networks. Studies of other connective tissue diseases associated with depression have found that elevated proinflammatory cytokines and decreased anti-inflammatory cytokines can lead to neuroendocrine disorders and abnormal neurobiochemical metabolism, thereby promoting the formation of depressive symptoms. These conclusions also need to be validated in a disease model of pSS.

For management, comprehensive treatment, including drug therapy, psychological intervention, exercise therapy and health education, could hopefully alleviate patients' depression; improve pSS symptoms such as sicca syndrome, fatigue and pain; and improve patients' QoL. An increasing number of studies have shown that TCM conditioning can effectively improve the mood of patients, which provides a new idea for the future clinical decision-making of rheumatologists. However, current results on the efficacy of anti-inflammatory drugs for psychiatric symptom relief in patients with pSS are controversial, partly because of great heterogeneity between studies and inconsistencies between patient dosages and baseline inflammatory levels. Therefore, clinical trials with consistent test methods and patterns of medication use for rigorous evaluation of the overall efficacy of treating depressive pSS patients with anti-inflammatory drugs are needed in the future. Moreover, at present, there is no specific psychological education intervention for pSS patients with depression, and the formulation of these interventions and the evaluation of their efficacy need further research.

Notably, gene polymorphisms and expression profiles could also account for the pathogenesis of pSS comorbid with depression, which has been reported by a few studies (94, 95). Therefore, genomic studies, combined with other techniques including transcriptomics, proteomics, and metabolomics, might help researchers find specific biomarkers that could reflect CNS immune status and identify depression in pSS patients. In addition, since dysbiosis of gut microbiota is found in both pSS and depression patients (96, 97), whether similar microbiota compositions are shared in these patients and lead to the development of mood disorders in pSS patients is worth exploring.

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