



Psychiatric Symptoms in Systemic Lupus Erythematosus: Diagnosis and Treatment

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According to the American College of Rheumatology classification, lupus erythematosus has five psychiatric manifestations, including cognitive dysfunction, mood disorder, anxiety disorder, psychosis, and acute confusional state, which are frequently accompanied by other symptoms. Cognitive dysfunction is the most common psychiatric manifestation in lupus patients with a prevalence rate ranging from 20% to 80%. The expression of psychiatric manifestations has been considered to be associated with disease activity, side effects of medications, and/or psychosocial stresses from the chronicity of lupus, but this has not been fully understood. Appropriate management of psychiatric symptoms is essential as it affects treatment adherence and quality of life. This review aimed to facilitate understanding of psychiatric manifestations of lupus through literature review on the prevalence, clinical features, diagnosis, and treatments of each psychiatric symptom. (*J Rheum Dis* 2019;26:93-103)

Key Words. Lupus erythematosus, systemic, Mental disorders, Diagnosis, Therapeutics

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease affecting multiple organ systems, which also involves the nervous system. It was characterized by the production of autoantibodies that target self-antigens and the occurrence of immune complexes that could accumulate in tissues and cause systemic inflammation [1]. Over the past few decades, clinicians have become more aware of the sequelae of the disease [2]. Nowadays, clinicians have realized that a great portion of lupus patients had suffered from psychiatric symptoms [1]. According to the meta-analysis performed by Unterman et al. [3], the prevalence of mood disorder or cognitive dysfunction was approximately 20% in patients with SLE. Psychiatric symptoms itself were distressful, which led to a decreased quality of life [4,5]. Moreover, the presence of psychiatric symptoms seemed to be related to increased disease activity of SLE and risk of complications, such as cardiovascular disease [6,7], as

well as medication nonadherence. A study found that depression was associated with higher risk of cardiovascular disease with odds ratio of 3.85 after adjusting for other risk factors. The authors suggested that behavioral pathway (negative change of life style due to depression) or biological pathway (inflammatory factor or adiposity which of both were known to have bidirectional effect with depression and important factor for cardiovascular disease) can be the possible explanation of increased risk of cardiovascular disease in depressed SLE patients, but not fully understood yet [7]. A recent systematic review found that one of the four determinants of nonadherence was depression; other factors were rural residence, lower education level, and polypharmacy [8]. Thus, proper detection and management of psychiatric symptoms with comprehensive understanding of their pathogenesis and pathophysiology are required. According to the American College of Rheumatology (ACR) classification, psychiatric manifestations of lupus included the following central nervous system (CNS) syndromes: cognitive dys-

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function, mood disorder, anxiety disorders, psychosis, and acute confusional state [9]. This review aimed to improve the understanding of the diagnosis and management of each psychiatric symptom, and a literature review on each psychiatric symptom has been conducted.

MAIN SUBJECTS

General consideration

Psychiatric symptoms can be a manifestation of SLE, which also involves the CNS. Vascular injury mediated by antiphospholipid antibodies or immune complexes and autoimmune/inflammatory reaction accompanied by increased blood-brain barrier permeability have been proposed as a mechanism of neuropsychiatric manifestations [10]. The ACR published a set of neuropsychiatric SLE (NPSLE) case definitions in 1999 [9], which identified 7 peripheral and 12 CNS manifestations associated with lupus (Table 1). NPSLE was one of the most important manifestations of lupus [9], which developed in 20%~70% of patients during the course of the disease [11]. In the ACR classification, there are five psychiatric manifestations included in CNS syndromes: cognitive dysfunction, mood disorder, anxiety disorders, psychosis, and acute confusional state [9]. However, the attribution of psychiatric symptoms in lupus is varied and complex, and the pathogenesis is not yet fully understood. Not only pathophysiology of the disease [12] but also adverse effects of corticosteroids [13] and psychosocial stressors associated with the chronicity of the disease would attrib-

ute to psychiatric symptoms [14].

1) General diagnostic approach

It is challenging to differentiate between functional and organic causes of psychiatric manifestations [15]. Hence, decision rules for attribution has been proposed using interval between onset of neuropsychiatric symptoms and the diagnosis of SLE, concurrent non-SLE factors, potential causes (“exclusions”) or contributing factors (“associations”) identified in the ACR glossary, and considering the events which are frequent in the general population [10]. Recently, Bortoluzzi et al. [16] developed algorithm for attribution with cut-off point of 6. According to the algorithm there are 4 items incorporated: i) Temporal relationship between onset of neuropsychiatric symptom and SLE - neuropsychiatric symptom before more than 6 months to SLE onset scores 0, within 6 months of SLE onset scores 3, and after more than 6 months after SLE onset scores 2; ii) whether the neuropsychiatric symptoms are one of the non-specific and common features, such as headaches, anxiety, mild form of depression or cognitive impairment and polyneuropathy without electrophysiological conformation - if yes scores 0 and if no scores 3; iii) presence of confounding factors or not SLE related associations - none or not applicable scores 2, present of one factor scores 1 and present of more than one factors scores 0; iv) presence of additional favouring factor - none or not applicable scores 0, present of one factor scores 1 and present of more than one factors scores 2. However, it is still challenging to differentiate between the primary psychiatric disorder and NPSLE because both use exclusion of other conditions as diagnostic criteria and psychiatric symptoms can result from multiple factors. Regardless of attribution, neuropsychiatric symptoms were reported to reduce the quality of life and increase organ damage [17]. Psychiatric manifestations vary in presentation and severity among patients [1]. These manifestations could be the initial symptoms of lupus or could occur at any time during the course of the disease [18].

Since there is no gold standard in the diagnostic approach of NPSLE, there are no other options but to diagnose through the diagnosis of exclusion. In all patients, the other causes, such as infection, metabolic abnormalities, or drug side effects, should be excluded first [19]. The European League against Rheumatism guidelines recommended performing initial diagnostic work-up like in non-SLE patients with similar manifestations [20]. Thus, for psychiatric manifestations, thorough psychi-

Table 1. Classification of neuropsychiatric syndromes in systemic lupus erythematosus

Central nervous system		Peripheral nervous system
Focal symptoms	Diffuse symptoms	
Aseptic meningitis	Cognitive dysfunction	Guillain-Barre syndrome
Cerebrovascular disease	Mood disorder	Autonomic disorder
Demyelinating syndrome	Anxiety disorder	Mononeuropathy
Headache	Acute confusional state	Myasthenia gravis
Movement disorder	Psychosis	Cranial neuropathy
Myelopathy		Plexopathy
Seizure disorder		Polyneuropathy

Based on the 1999 American College of Rheumatology case definitions for neuropsychiatric lupus syndrome [9].

atric history must be obtained, including chronological description of evolution of current symptoms, fluctuations in the nature or severity of those symptoms, presence or absence of stressors, factors that alleviate or exacerbate symptoms, past psychiatric history, substance use, family history, developmental and social history, and mental status examination [21]. Neurological assessment should include alertness, headache, signs of seizures, and motor and sensory deficits, and psychiatric evaluation should include behavior, cognition, thought, perception, and mood and affect [19]. Psychiatric rating scales may be considered depending on the chief manifestation, such as the Brief Psychiatric Rating Scale for psychosis, Beck Anxiety Inventory (BAI), and Hamilton Rating Scale for Depression (HDRS). Formal neuropsychological tests, such as Mini-Mental State Examination (MMSE), Boston Naming Test, and Wisconsin Card Sorting Test are helpful in the assessment of cognitive

dysfunction (Table 2).

Although various clinical, laboratory, and radiographic findings have been reported to be potentially beneficial for the differential diagnosis of NPSLE, there is no sensitive or specific single diagnostic test at present [1]. The proper diagnosis depended on the combination of rheumatologic exam, brain imaging, and serological and neuropsychological tests in the presence of disease activity [18]. Cerebrospinal fluid (CSF) analysis and electroencephalography (EEG) can be considered depending on clinical manifestations. For magnetic resonance imaging (MRI) protocol, conventional sequence with diffusion-weighted imaging and gadolinium-enhanced T1 sequence was recommended [20].

2) General management

Management of psychiatric symptoms is generally immune/inflammation or thrombotic cerebrovascular dis-

Table 2. Diagnostic approach for psychiatric manifestations in systemic lupus erythematosus

All patients	Measure disease activity* Therapeutic history*: psychoactive drugs, immunosuppressants Laboratory tests*: autoantibodies, complete blood count, serum chemistries including liver and renal function tests, thyroid function, urinalysis Thorough psychiatric history [†] : chronological description of evolution of the current symptoms, fluctuations in the nature or severity of those symptoms, presence or absence of stressors, factors that alleviate or exacerbate symptoms, past psychiatric history, substance use, family history, developmental and social history
Cognitive dysfunction	Structural neuroimaging studies*: Exclude infection, infarction, malignancy, and other neurological diseases Additional laboratory tests*: B ₁₂ and folate level, exclude diabetes and infectious diseases Psychological tests [†] Attention: Conners' continuous performance test, Visual search and attention test Memory: California verbal learning test II, Warrinton recognition memory test for faces Language: Boston diagnostic aphasia examination, Boston naming test Visual perception: Hooper visual organization test, judgment of line orientation test Constructional abilities: complex figure test, Wechsler adult intelligence scale-IV block design Executive function: category test, Delis-Kaplan executive function system sorting test, Wisconsin card sorting test
Mood disorders	Neuroimaging required if neurological symptoms or signs are present [†] Psychological tests [†] : Beck depression inventory, geriatric depression scale, Hamilton rating scale for depression, manic-state rating scale, suicide intent scale
Anxiety disorder	Additional laboratory tests: Exclude thyroid disease and pheochromocytoma Psychological tests [†] : Beck anxiety inventory, State-trait anxiety inventory
Acute confusional state [†]	Structural neuroimaging studies: Exclude infection, malignancy, and other neurological diseases Additional laboratory tests: Exclude infectious diseases Cerebrospinal fluid analysis: Exclude infectious diseases
Psychosis	Neuroimaging required if neurological symptoms or signs are present [†] Psychological tests [†] : Brief psychiatric rating scale, Positive and negative syndrome scale

Adapted from *Liang-Checa C, et al. *Drugs* 2016;76:459-83 [19], [†]Kupfer. American Psychiatric Publishing 2014 [21], and

[†]Bertsias GK, et al. *Ann Rheum Dis* 2010;69:2074-82 [20].

ease targeted, especially when non-SLE-related causes were excluded, such as glucocorticoids and immunosuppressive therapy or antiplatelet/anticoagulation therapy. Symptomatic management, such as antidepressants or antipsychotics, and the treatment of aggravating factors should also be considered [20].

Cognitive dysfunction

The prevalence of cognitive dysfunction among lupus patients was high, ranging from 20% to 80% [3,22], which was more than two times higher compared with the general population [22]. Severe cognitive impairment developed in a smaller proportion of patients, generally 3%~5% [20]. In a recent big data study in Israel, dementia was found to be significantly more prevalent in patients with SLE than in the general population with the odds ratio of 1.5 [23]. The most frequently affected cognitive domains were visual and verbal memory, attention, executive function, and psychomotor speed [24]. In the majority of patients, cognitive dysfunction was not cumulative over time and their test performance indicated almost stable dysfunction [25].

Cognitive dysfunction does not seem to be directly attributable to lupus activity, disease burden, or corticosteroid therapy [26]. It could occur in the absence of either serological activity or other systemic manifestations and fluctuate over the course of the disease [27]. Symptoms could be compounded by several confounding factors, such as fatigue, pain, sleep deprivation, medications, depression, and anxiety [1,19]. Immune suppressants (e.g., cyclophosphamide or azathioprine) may cause anemia, headache, fatigue, nausea, and cognitive impairment [28]. Cortical atrophy and subcortical and periventricular white matter hyperintensities have been found in the brain MRI of lupus patients, but these abnormalities did not correlate with the severity of cognitive impairment [29]. More severe cognitive dysfunction in lupus patients may be associated with antiphospholipid syndrome (APS) [30]. Persistent elevation of anti-cardiolipin (aCL) antibodies over 1~5 years was associated with long-term subtle deterioration of cognitive function [31]. Higher levels of lupus anticoagulant (LA), aCL-IgG antibodies were associated with higher risk of CNS involvement at the onset of lupus [32]. APS was definitely associated with multiple ischemic stroke and vascular dementia [33] and contributed to significant morbidity [34].

1) Diagnostic approach

Screening of cognitive dysfunction and assessment of cognitive function have been performed in SLE using neuropsychological scales. In SLE studies on cognitive dysfunction, Automated Neuropsychological Assessment Metrics (ANAM) was most frequently utilized, along with other scales, such as MMSE, Montreal Cognitive Assessment (MoCA), Controlled Oral Word Association Test (COWAT), and the Hopkins Verbal Learning Test-Revised [35]. However, ANAM was reportedly time-consuming and not suitable for screening in clinical settings [36], while MMSE and MoCA were brief and well validated and hence widely used in clinics. Especially, recent studies found that MoCA is useful for patients with SLE with higher sensitivity than MMSE and also found comparable results with ANAM [36,37]. More detailed cognitive assessment battery, such as Consortium to Establish a Registry for Alzheimer's disease or specific assessment tools for each cognitive domain, has generally been offered for patients with cognitive decline, but these tools were not studied or validated in patients with SLE [38].

Brain MRI should be considered for patients under 60 years of age, unexplained rapid or significant cognitive decline, recent head trauma, new-onset neurological signs and symptoms, or development of symptoms during immunosuppressive or antiplatelet/anticoagulation therapy [20].

2) Management

No consistent evidence-based therapy exists for cognitive impairment in lupus [19]. For patients who have cognitive dysfunction with depression, antidepressants may be administered [39]. Psychoeducational group intervention combined with functional strategy training and psychosocial support, which conducted weekly 2-hour sessions for 8 weeks, was reported to have positive effects on memory function and the ability to perform daily activities of lupus patients aged 25~60 years who have reported distress consequent to their cognitive difficulties [40].

The role of pharmacologic treatment in cognitive impairment remained uncertain [41]. In a randomized, double-blind placebo-controlled 12-week trial of memantine for 51 lupus patients who had cognitive impairment [42], it did not exhibit significant improvement in cognitive function compared with the placebo group, with the exception of COWAT. In those with APS patients, anti-

coagulation was warranted [43]. In vascular dementia, acetylcholine esterase inhibitors, such as donepezil or memantine, are generally prescribed. Cholinesterase inhibitors increase acetylcholine availability and enhance cholinergic neurotransmission by decreasing the cholinesterase-mediated degradation of acetylcholine in the synaptic cleft. Memantine is proposed to reduce chronic activation by acting as an N-Methyl-D-Aspartate (NMDA) receptor antagonist. Chronic activation of CNS NMDA receptors has been suggested to be partially responsible for the neurodegeneration [21].

Mood disorders

Mood disorders in lupus included major depressive-like episodes and mood disorders with depressive, manic, or mixed features [1]. The most common mood disorder in lupus patients was depression, ranging from 11% to 39% [44], while mania was much less common, which was reported to be present in approximately 3% [12]. According to Ainiala et al. [22], there was four times higher prevalence of depression in lupus patients compared with that in a matched control group. The most frequently reported depressive symptoms in lupus were fatigue and weakness (88%~90%), irritability (82.3%), somatic complaints (76%), sleep disturbances (70%), and sadness (29%~73%) [45]. It is important to remember that depression may cause medication nonadherence and could lead to impaired optimal management of lupus [46]. The prevalence of suicide ideation was much higher in lupus patients compared to the general population, ranging from 10% to 34% [45,47]. The risk factors of suicide attempt in lupus patients included psychosis, insomnia, incompletely controlled disease, photosensitivity, tapering corticosteroid doses, major life events in the last month, previous suicide attempt, diffuse slowing on electroencephalogram, and hypocomplementemia [48,49].

Direct CNS involvement, comorbid psychiatric disorders, recent usage of high-dose prednisone (20 mg or higher), and psychosocial stress from disease burden, including recent SLE diagnosis, were risk factors of depression in lupus [50,51]. Other contributing factors included higher anxiety, young age [52], non-Asian ethnicity, cutaneous disease, and longitudinal myelitis [51]. While some studies reported a significant correlation between depression severity and lupus activity [53], another study reported that no relationship was found between the presence of depressive episode and lupus activity [54].

Mood disorders were associated with the stress of suf-

fering from a chronic disease, such as its harmful effect on the quality of life, physical disability, and perceived lack of control over the disease [55]. Fatigue and joint pain could lead to functional disability and feelings of loss, inferiority, and inadequacy [44]. At least for some patients, lupus-related depression was associated with adverse effects of corticosteroid, which may have downregulated brain-derived neurotrophic factor and caused depression, mania, psychosis, insomnia, and mood swings [56]. In these cases, clinicians should consider to reduce corticosteroid doses or avoid its use [51]. Other patients may also present organic forms of depression caused by autoimmune lesion in the CNS. A relationship of depression and psychosis with specific antibodies, such as anti-ribosomal P antibody and anti-NMDA receptor antibody, has been suggested [57-59]. In a study that compared clinical and psychosocial characteristics between lupus patients, depressed patients, and rheumatoid arthritis patients, fatigue severity, relationship satisfaction, and interleukin-10 (IL-10) concentrations were indicators of depression in lupus patients [60].

1) Diagnostic approach

Validated rating scales were used in studies for screening depression in patients with SLE, such as HDRS, BDI, Hospital Anxiety and Depression Scale (HADS), and Center for Epidemiologic Studies Depression Scale (CES-D) [52,61-63]. As the diagnostic gold standard, a clinical assessment was performed that includes a diagnostic interview by mental health professionals, where patients with a high risk of depression from screening test were advised to visit mental health professionals. It is important to differentiate between mood disorders caused by lupus and primary mood disorders. Since neuropsychiatric manifestations of lupus have not commonly persisted in isolation for more than 18 months [64], if the onset of depressive symptoms precedes the diagnosis of lupus by at least 2 years, it should be considered as independent from lupus.

2) Management

Mood disorders were regarded as mild neuropsychiatric manifestations, which may require symptomatic treatment only [41]. Although selective serotonin reuptake inhibitors (SSRIs), which selectively inhibit serotonin reuptake [21], were considered the first-line treatment option for depression in lupus patients due to their safety and tolerability [18], treatments remained empirical due

to lack of controlled studies [44]. Escitalopram, fluoxetine, and paroxetine are reportedly effective in cases of depression associated with lupus [65-68]. Cognitive behavioral treatment, compared with conventional therapy, significantly reduced depressive symptoms in lupus patients [69]. A randomized controlled trial found that biofeedback-assisted cognitive behavioral treatment was superior to usual care for patients with SLE in terms of pain and psychological and perceived physical function [70].

Mania may be due to severe lupus activity or corticosteroid therapy [44]. In some cases, mania could be the first manifestation of lupus [71,72]. Valproic acid was preferred to avoid potential risk of nephrogenic diabetes insipidus associated with lithium [73]. Valproic acid binds to and inhibits γ -aminobutyric acid (GABA) transaminase, resulting in increased brain concentrations of GABA, an inhibitory neurotransmitter. Lithium influences several intracellular properties, including phosphoinositide metabolism, G proteins, and protein kinase activity, and it stimulates neurogenesis [21].

Anxiety disorder

Anxiety disorder was a common and early symptom of lupus [74], with a prevalence of up to 40%. Ainiala et al. [22] found that anxiety disorders were two times more prevalent among lupus patients compared to non-lupus population. Anxiety disorders associated with lupus included prominent anxiety, panic disorders (15.6%), obsessive-compulsive disorder (OCD) (8.9%), and generalized anxiety disorder (4.3%).

Like depression, anxiety also could be influenced by disease-related psychosocial stressors [44]. Basal ganglia abnormalities were suggested to be the pathophysiology of coexisting OCD and lupus, but exact mechanism of basal ganglia dysfunction in lupus remained unknown [75]. Anti-PO antibody and proteinuria were reported to be associated with anxiety in lupus patients [76].

1) Diagnostic approach

Studies used several validated rating scales for screening anxiety in patients with SLE, such as HADS, Hamilton Anxiety Scale, and BAI [77]. Each anxiety disorder could be differentiated through specific symptom manifestations acquired from psychiatric interview. In panic disorder, the individual experiences recurrent unexpected panic attacks. The key features of generalized anxiety disorder included persistent and excessive anxiety and worry about various domains. OCD is characterized by the pres-

ence of obsessions; recurrent and persistent thoughts, urges, or images that are experienced as intrusive and unwanted; and/or compulsions and repetitive behaviors or mental acts that are performed in response to an obsession [78].

2) Management

Anxiety disorders were regarded as mild neuropsychiatric manifestations, which may require symptomatic treatment only [41]. Antidepressants, such as SSRIs, and anxiolytics, such as benzodiazepines, can be prescribed according to the standard indications in primary psychiatric disorders. Benzodiazepines decrease neuronal excitability by binding to and activate GABAA receptor [21]. Since evidence-based data were scarce in psychiatric symptoms in lupus, treatments remained empirical [44].

Acute confusional state

Acute confusional state was one of the uncommon psychiatric manifestations that had been reported in 4%~7% of lupus patients [79]. Acute confusional state is a diffuse neurological dysfunction that was characterized by acute-onset and fluctuating level of consciousness, disorientation, diminished ability to focus attention, mood disturbances, and cognitive impairment. It is equivalent to delirium according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5).

1) Diagnostic work-up

The severity of acute confusional state in lupus patients could vary widely from mild confusion and mildly disturbed attention to profound disorganization with agitation and hallucinations [18]. Acute confusional state in lupus patients should be differentiated with other causes, such as CNS infection, metabolic abnormalities, or adverse effect of corticosteroids [20]. Altering the corticosteroid dosage was a prompt and beneficial manner to differentiate between acute confusional state due to lupus and corticosteroid-induced delirium [43]. Furthermore, vascular and hemorrhagic sequelae of CNS involvement by lupus, such as subarachnoid hemorrhage, lupus meningitis, or strokes could be associated with acute confusional state [80].

2) Management

Acute confusional state associated with lupus requires corticosteroid with antipsychotics, such as low-dose hal-

operidol (under 3 mg per day) or atypical antipsychotics, including risperidone, olanzapine, and quetiapine [81]. The typical antipsychotics including haloperidol and chlorpromazine have heterogeneous receptor effects; however, their primary therapeutic effect is via non-specific blockade of the dopamine D2 receptor subtype. The atypical antipsychotics are thought to exert more specific mesolimbic dopamine receptor blockade compared with the typical antipsychotics, combined with 5-hydroxytryptamine (5-HT; serotonin) type 2 (5-HT₂) receptor antagonism [21]. In refractory cases, cyclophosphamide [82], plasma exchange [83], and rituximab [84] were reported to be effective.

Psychosis

Lupus psychosis was uncommon, which could affect 2%~11% of lupus patients [85,86] and was characterized by paranoid delusion with visual auditory hallucination [80]. Generally, these manifestations presented early in the course of the disease [85], and most episodes resolved within 2~4 weeks [20]. Psychosis was usually associated with damage mediated by immune dysregulation, and metabolic disturbances or medications (e.g., corticosteroid) may be also involved [1]. It may be present in up to 31%~39% of patients with high-dose corticosteroid treatment [86]. And it should always be differentiated from schizophrenia and substance abuse [87].

1) Diagnostic approach

Corticosteroid-induced psychiatric disorders, including mood disorders, psychotic disorders, and delirium, should be carefully distinguished from primary NPSLE [41]. It typically started 5~14 days after initiation or increased dose of corticosteroid therapy, was dose dependent, and regressed with steroid discontinuation [41]. Factors that reportedly increase the risk of corticosteroid-induced psychiatric disorders included high-dose corticosteroid (daily prednisone equivalent dose of over 40 mg), women, first 6 weeks after initial treatment [88], hypoalbuminemia [89], low complement, and elevated CSF/serum albumin ratio [90].

Elevated titers of anti-ribosomal P antibodies have been demonstrated to be a clinically useful biomarker in lupus psychosis [91], but it had limited diagnostic accuracy [92]. Abnormal findings in MRI, such as increased signal intensity in the right frontal white matter with mild cortical atrophy, reduced brain perfusion, and EEG had been found in some patients with lupus psychosis [86]. Brain

imaging was recommended especially when patients have additional neurological signs and symptoms [20].

2) Management

Lupus psychosis usually correlated with disease activity and improved with immunosuppressive therapy, corticosteroids, and low-dose antipsychotics [86,93]. On first episode psychosis, the use of antipsychotic agent was recommended, in which chlorpromazine and haloperidol were most commonly used [86]. In a study that reviewed medical records retrospectively, 36 episodes from 750 lupus patients were treated with a combination of immunotherapy and haloperidol, risperidone, and quetiapine in 23, 4, and 2 episodes, respectively [94]. Olanzapine was reportedly effective in several cases of lupus psychosis [95,96]. In a case series, 10 children inpatients aged 10~19 years with acute lupus psychosis were successfully treated with risperidone, quetiapine, and olanzapine [97]. Recovery was complete but commonly relapsed [18]. In refractory or relapsing cases, immunosuppressive therapy was required [41]. Electroconvulsive therapy (ECT) also reported to be safely and effectively used and played a role in the resolution of symptoms in refractory cases of lupus psychosis [98,99].

3) Catatonia

There exist numerous case reports of catatonia as a complication of lupus. The DSM-5 diagnosis criteria of catatonia include three or more features of the following: cataplexy, waxy flexibility, stupor, agitation, mutism, negativism, posturing, mannerisms, stereotypies, grimacing, echolalia, and echopraxia [78]. It can be a manifestation of neuropsychiatric lupus, particularly with laboratory values that indicate acute lupus flares at the time of presentation. In most of the cases, catatonia was improved with immunosuppressive therapy [100] and worsened with antipsychotic medications, including precipitating neuroleptic malignant syndrome; hence, recognition of catatonia is important [101]. Benzodiazepines were the first-line treatment for catatonia, and ECT was used for catatonia refractory to benzodiazepines [102].

CONCLUSION

Neuropsychiatric symptoms are common in lupus patients, and their recognition is important. There are five psychiatric symptoms according to the ACR classification: cognitive dysfunction, mood disorder, anxiety

disorders, psychosis, and acute confusional state. The pathogenesis, exact role of specific antibodies, and attribution of psychiatric symptoms in lupus patients were not well understood yet. Since psychiatric symptoms are common and require timely and appropriate management, psychiatric screening would be helpful in patients who were first diagnosed with lupus. It is important to differentiate between primary and secondary psychiatric disorders. And in psychiatric symptoms in lupus, the diagnostic approach should be taken similar to that of psychiatric patients without lupus. Treatment was generally selected according to the psychiatric symptom, but immunosuppressants may help in severe or refractory cases. Since controlled trials are scarce yet, further studies are needed in the future to develop individualized therapies. The development of accurate diagnostic methods also helps to select appropriate therapies.

Appropriate evaluation and treatment of psychiatric symptoms in lupus patients affect the adherence, prognosis, and quality of life. As the initial diagnostic approach and management include that of psychiatric patients without lupus, it is necessary to collaborate with psychiatrists for optimal lupus patients' care.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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