Psychiatric Symptoms in Systemic Lupus Erythematosus: A Systematic Review

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ABSTRACT

Objective: Systemic lupus erythematosus (SLE) presents with psychiatric symptoms in most patients that often remain undiagnosed and untreated. This study evaluates the prevalence of psychiatric symptoms in SLE on the basis of clinical trials that fulfilled diagnostic criteria specified by the American College of Rheumatology (ACR). Current hypotheses explaining the pathogenesis of psychiatric symptoms of lupus are reviewed to gain new insights into the neuroimmune pathogenesis of other psychiatric disorders.

Data Source: A MEDLINE search of the literature (English language only) from April 1999 to August 2011 was performed using the search terms *lupus* and *psychiatric* to identify studies of neuropsychiatric SLE.

Study Selection: Of 163 publications, 18 clinical studies were selected that focused on psychiatric symptoms, had a sample size of at least 20, and included patients of any age or gender as long as they fulfilled ACR criteria for neuropsychiatric SLE.

Data Extraction: The following data were extracted: author name, year of publication, psychiatric diagnostic method, total number of patients with SLE, and percentage of patients with individual psychiatric diagnoses. The point prevalence of psychiatric symptoms was calculated for neuropsychiatric SLE diagnoses in every study included.

Results: Psychiatric symptoms are present in the majority of patients with SLE. Depression (in up to 39% of patients) and cognitive dysfunction (up to 80%) are the most common psychiatric manifestations. Genetic and environmental factors (eg, ultraviolet light, retroviruses, and medications) may play a role in the pathogenesis. In addition, the patient's reaction to the illness may result in anxiety (up to 24%) and depression. Currently known biomarkers are nonspecific for neuropsychiatric SLE and indicate inflammation, microglial activation, ischemia, oxidative stress, mitochondrial dysfunction, and blood-brain barrier dysfunction.

Conclusions: Identification of lupus-specific biomarkers of psychiatric symptoms is a high priority. Our current diagnostic assessment methods need improvement. Development of evidence-based guidelines is needed to improve diagnosis, prevention, and treatment of disabling psychiatric complications in lupus.

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Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disorder that may affect multiple organ systems, including the central nervous system (CNS). The clinical course is marked by spontaneous relapses and remissions. According to the American College of Rheumatology (ACR) nomenclature published in 1999,[1] there are 19 peripheral and CNS syndromes that are associated with lupus (Table 1). Five of the CNS symptoms are psychiatric symptoms: acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, and psychosis.

Systemic lupus erythematosus affects from 161,000 to 322,000 adults in the United States. Mean annual direct cost of treatment is $13,000 to $21,000 per patient.[2] The prevalence of SLE is influenced by gender and race: 80%–90% of patients are women, and SLE is more prevalent in African American, Hispanic, Asian, and American Indian women compared to white women. In the United States, SLE occurs in 1 in 1,000 white women, 1 in 250 African American women, and 1 in 9,000 men.[3] The incidence and prevalence of SLE vary considerably across countries and are higher in Europe as compared to the United States. The highest prevalences were reported in Sweden, Iceland, and Spain.[4] Systemic lupus erythematosus usually develops after menarche and before menopause.

Neuropsychiatric SLE develops in 20%–70% of SLE patients during the course of their disease.[5] Even though SLE presents with a wide variety of treatable psychiatric symptoms, patients rarely seek and receive adequate treatment. Patients with SLE usually do not receive a detailed psychiatric assessment during their initial evaluation. Specific guidelines for the treatment of psychiatric symptoms in SLE are lacking. Patients are often unaware of their cognitive impairment[6]; hence, they do not report them and do not seek treatment.

Overlooking psychiatric symptoms may have severe consequences for the patient, eg, decreased quality of life, disability, loss of employment, disruption of supportive relationships, and stigma and shame, any of which, in turn, can worsen depression and other psychiatric symptoms.

Our goal was to summarize observations on the prevalence of psychiatric symptoms in lupus. Current hypotheses explaining the pathogenesis of psychiatric symptoms of lupus were reviewed to gain new insights into the neuroimmune pathogenesis of other psychiatric disorders. Clarification of the pathogenesis of psychiatric symptoms in SLE may provide new treatment options for a subset of psychiatric disorders associated with immune dysfunction. Biomarkers associated with psychiatric symptoms in lupus were summarized, and their clinical significance was discussed. Early detection of psychiatric symptoms in SLE is very important, because without treatment, serious psychiatric complications often lead to disability.

Clinical Points

- Depression and cognitive dysfunction are the most common psychiatric manifestations in systemic lupus erythematosus (SLE).
- Psychiatric symptoms occur in half of SLE patients before diagnosis of their disease.
- In female patients with new-onset depression, cognitive dysfunction, or psychosis *and* family history of SLE, determination of antinuclear antibody titer might help clinicians to raise the possibility of neuropsychiatric SLE.

DATA SOURCES AND STUDY SELECTION

A MEDLINE literature search from April 1999 to August 2011 was performed to identify studies of neuropsychiatric SLE, using the search terms *lupus* and *psychiatric*. The selection criteria were as follows: all clinical trials with human subjects were included if they had a sample size of at least 20; only English-language studies that focused on psychiatric symptoms were included; and patients of any age or gender were included as long as they fulfilled ACR criteria for SLE. Of 163 publications, 18 clinical studies were selected to be included in the review (Table 2). The following data were extracted: author name, year of publication, psychiatric diagnostic method, total number of patients with SLE, and number (or percentage) of patients with individual psychiatric diagnoses. The point prevalence of psychiatric symptoms was calculated for each diagnosis in every study included. In addition, all 163 publications were reviewed to identify hypotheses and biomarkers of psychiatric symptoms in SLE.

PREVALENCE OF NEUROPSYCHIATRIC SYMPTOMS IN LUPUS

Major depression and cognitive dysfunction (impaired attention, memory deficit, and impaired executive function) are the most common psychiatric manifestations in patients with lupus[7] (see Table 2). Both depression and cognitive dysfunction may lead to impaired occupational functioning. Depression was found to be present and associated with cognitive impairment in newly diagnosed SLE (less than 9 months since diagnosis).[7]

Table 2 presents the point prevalence of psychopathology and cognitive dysfunction among SLE patients. Most studies of neuropsychiatric phenomena in SLE did not include a control group of non-SLE patients. In a review[8] of 21 other studies published before the development of the neuropsychiatric SLE criteria by the American College of Rheumatology in 1999,[1] substantial differences in the prevalence of psychiatric symptoms were found (17%–71%).[8] Only a minority of studies applied control groups or standardized assessments, and most were based on chart reviews. In these studies, disease severity and medications were usually not taken into account. Four studies used patients with rheumatoid arthritis as controls and described striking similarities in the prevalences of depression and anxiety in the rheumatoid arthritis and SLE groups.[9–12]

Table 1. Nineteen Neuropsychiatric Systemic Lupus Erythematosus Syndromes Identified by the American College of Rheumatology[a]

Peripheral Nervous System	Central Nervous System
1. Guillain-Barré syndrome	1. Aseptic meningitis
2. Autonomic disorder	2. Cerebrovascular disease
3. Mononeuropathy	3. Demyelinating syndrome
4. Myasthenia gravis	4. **Headache**
5. Neuropathy, cranial	5. Movement disorder/chorea
6. Plexopathy	6. Myelopathy
7. Polyneuropathy	7. Seizure disorder
	8. Acute confusional state
	9. Anxiety disorder
	10. **Cognitive dysfunction**
	11. **Mood disorder**
	12. Psychosis

[a]Adapted from the American College of Rheumatology (ACR).[1] Symptoms present in more than 50% of patients are in bold type. Fatigue, posterior reversible encephalopathy, and reversible focal neurologic deficit are not listed as neuropsychiatric syndromes by the ACR.

Depression is present in 11%–39% of patients and may be the first symptom before diagnosis of SLE.[13] Ainiala et al[14] found a 4 times higher prevalence of depression in SLE compared to a matched, non-SLE population. Due to different assessment methods (self-report vs psychiatric interview vs standardized rating scales), different diagnostic criteria (major depression based on *DSM-IV* criteria vs Beck Depression Inventory scores vs presence of depressed mood), and different patient populations, the prevalence of depression varies considerably among studies.

In patients with SLE, it is important to distinguish between mood disorder due to a general medical condition (SLE) and major depressive disorder, in which the symptoms are not secondary to a medical condition or to the physical effects of a substance (eg, alcohol, recreational drugs, or medications). Since neuropsychiatric symptoms of lupus rarely persist in isolation for more than 18 months,[15] if the onset of depression precedes the diagnosis of SLE by at least 2 years, major depressive disorder is the correct diagnosis.

Jarpa et al[16] found that 9.5% of 83 patients with SLE were at risk of suicide, which far exceeded the risk in the general population.

Mania is present in approximately 3% of patients.[17] Mania may be a result of severe lupus disease activity or corticosteroid treatment. Several case reports confirm that mania can be the first manifestation of lupus.[18,19]

Cognitive impairment (impaired attention, memory, and executive function) is often detected in SLE patients (see Table 2), with a prevalence more than 2 times higher in this group as compared to the general population.[14] Learning deficits are present in patients with lupus.[20] Cortical atrophy and subcortical and periventricular white matter hyperintensities were found (usually in the frontal-parietal regions) on magnetic resonance imaging (MRI) brain scans of SLE patients, but these quantitative MRI abnormalities did not correlate with the severity of cognitive deficits.[21]

Table 2. Point Prevalence of Psychiatric Symptoms in 18 Studies of Systemic Lupus Erythematosus (SLE)

Author	Year of Publication	Diagnostic Method	Number of Patients	Point Prevalence of Psychiatric Symptoms in SLE (controls), %
Cognitive dysfunction without anxiety or depression				
Maneeton et al[68]	2010	Neuropsychological testing,[a] Hamilton Anxiety Rating Scale, Hamilton Depression Rating Scale	30	30 (controls, 0)
Cognitive dysfunction				
Hawro et al[38]	2010	Mini-Mental State Examination, Clock Drawing Test	52	10
Brey et al[17]	2002	Automated Neuropsychological Assessment Metrics	128	79
Ainiala et al[14]	2001	Neuropsychological testing[b]	46	80 (controls, 28)
Afeltra et al[69]	2003	Neuropsychological testing[c]	61	52
Lapteva et al[44]	2006	Neuropsychological testing[d]	60	47
Harrison et al[70]	2006	Neuropsychological testing[e]	93	52
Antonchak et al[71]	2011	Automated Neuropsychological Assessment Metrics	31	19 (RA controls, 3)
Vogel et al[6]	2011	Neuropsychological testing[f]	57	39
Petri et al[7]	2010	Automated Neuropsychological Assessment Metrics	111	5
Hanly et al[72]	2005	Cognitive Symptoms Inventory; if abnormal, then neuropsychological assessment	53	2
Dementia				
Schenatto et al[73]	2006	Mini-Mental State Examination	23	13
Depression				
Ainiala et al[14]	2001	Beck Depression Inventory	46	39 (controls, 9)
Brey et al[17]	2002	Structured Clinical Interview for *DSM-IV* Axis I Disorders, Calgary Depression Scale	128	28
Petri et al[7]	2010	Calgary Depression Scale	111	31
Lapteva et al[44]	2006	Beck Depression Inventory-II	60	18
Harrison et al[70]	2006	Centers for Epidemiologic Studies Depression Scale	93	16
Jarpa et al[16]	2011	Mini-International Neuropsychiatric Interview-Plus, Hospital Anxiety and Depression Scales	83	22
Julian et al[74]	2011	Centers for Epidemiologic Studies Depression Scale	663	17
Hanly et al[72]	2005	Hospital Anxiety and Depression Scales	53	11
Mixed mood symptoms				
Ainiala et al[14]	2001	Clinical interview	46	4 (controls, 0)
Mood disorder				
Afeltra et al[69]	2003	Neuropsychological testing[g]	61	27
Brey et al[17]	2002	Structured Clinical Interview for *DSM-IV* Axis I Disorders	128	23
Gerli et al[75]	2002	Clinical interview	149	58
Anxiety				
Petri et al[7]	2010	American College of Rheumatology case definition	111	5
Brey et al[17]	2002	Structured Clinical Interview for *DSM-IV* Axis I Disorders, Hamilton Anxiety Rating Scale	128	24
Jarpa et al[16]	2011	Hospital Anxiety and Depression Scales	83	16
Hawro et al[38]	2010	Clinical interview	52	8
Ainiala et al[14]	2001	Clinical interview	46	13 (controls, 6.5)
Gerli et al[75]	2002	Clinical interview	149	15
Harrison et al[70]	2006	Spielberger State-Trait Anxiety Inventory	93	6
Hanly et al[72]	2005	Hospital Anxiety and Depression Scales	53	6
Acute confusion				
Ainiala et al[14]	2001	Clinical interview	46	7 (controls, 0)
Psychosis				
Petri et al[7]	2010	American College of Rheumatology case definition	111	3
Brey et al[17]	2002	Structured Clinical Interview for *DSM-IV* Axis I Disorders	128	5
Jarpa et al[16]	2011	Mini-International Neuropsychiatric Interview-Plus, Confusion Assessment Method	83	1
Hawro et al[38]	2010	Clinical interview	52	2
Appenzeller et al[23]	2008	Clinical interview	520	17
Schenatto et al[73]	2006	Clinical interview	23	39
Massardo et al[76]	2002	Chart review	141	1
Pego-Reigosa and Isenberg[22]	2008	Chart review	485	2.3
Gerli et al[75]	2002	Clinical interview	149	0.6

[a]Attention, calculation, auditory comprehension, visuospatial ability, and executive function were assessed.
[b]Wechsler Adult Intelligence Scale-Revised, Wechsler Memory Scale-Revised, California Verbal Learning Test, Continuous Performance Task, Wisconsin Card Sorting Test-Computer Version 2, Delis-Kaplan Executive Function System.
[c]Attention, memory, visual-spatial processing, language, reasoning, psychomotor speed, and executive function were assessed.
[d]California Verbal Learning Test; Rey-Osterrieth Complex Figure Test; Stroop Color, Word, and Color-Word Tests; Wechsler Adult Intelligence Scale; Trail Making Test B; Controlled Oral Word Association Test; and Grooved Pegboard Test.
[e]Attention, verbal and nonverbal memory, and visuospatial, psychomotor, and executive functions were assessed.
[f]Vocabulary of Wechsler Adult Intelligence Scale, Selective Reminding Test, Rey-Osterrieth Complex Figure Test, Trail Making Test A and B, Symbol Digit Modalities Test, Digit Span, Category Fluency, and Phonological Fluency.
[g]Brief Psychiatric Rating Scale, Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, and Clinical Global Impressions.
Abbreviation: RA = rheumatoid arthritis.

Anxiety disorders (generalized anxiety disorder and panic disorder) are also common. Ainiala and colleagues[14] found that anxiety disorders were twice as prevalent among SLE patients as compared to controls.

Psychosis is diagnosed in 2%–3% of SLE patients but may be present in up to 31%–39% of patients on high-dose corticosteroids.[22] In a large cohort of 520 lupus patients, Appenzeller and colleagues[23] identified 28 patients (5%) with corticosteroid-induced psychosis. These patients represented approximately one-third of acutely psychotic cases in their cohort. Chau and Mok[24] confirmed this finding; they also found corticosteroid-induced psychosis in 5% of 92 patients. Paranoid delusions and auditory and visual hallucinations may occur. In a large study of lupus psychosis,[23] 19 of 89 patients (21%) presented with psychotic symptoms at the onset of SLE. Psychotic lupus patients usually improve on treatment with corticosteroids, immune modulators, and low-dose antipsychotics,[22] and they frequently develop extrapyramidal side effects on higher neuroleptic doses. Psychosis seems to be specific to SLE. Lim and colleagues[12] found a 10% prevalence of psychosis in SLE patients compared to rheumatoid arthritis patients (0%).

Attention-deficit/hyperactivity disorder (ADHD) symptoms are also prevalent in SLE. In a recent pilot study[25] (N = 34), our group found elevated ADHD Self-Report Scale scores in female SLE patients compared to age- and sex-matched healthy controls. Symptoms of ADHD were associated with 1 measure of disease activity (the Safety of Estrogen in Lupus Erythematosus National Assessment [SELENA] Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] score) and with fatigue (Fatigue Assessment Scale).

PATHOGENESIS OF PSYCHIATRIC SYMPTOMS IN LUPUS

The pathogenesis of psychiatric symptoms in lupus is not well understood. Both genetic and environmental factors (eg, endogenous retroviruses, ultraviolet light, certain medications, and stress) may play a role.

Environmental insults are detectable on the molecular level (eg, DNA demethylation due to ultraviolet light), cellular level (eg, neuronal damage related to ischemia or inflammation elicited by cytokines and autoantibodies), or organ level (eg, blood-brain barrier dysfunction). Depression and anxiety may also be present (without detectable molecular, cellular, or organ damage) as a reaction to a serious (often fatal) recurring, painful illness, which is associated with visible symptoms such as insomnia, fatigue, and limited functioning.

Neuronal loss or dysfunction is often present in patients with cognitive dysfunction and is usually associated with vasculopathy, coagulopathy, ischemia, blood-brain barrier dysfunction, autoantibody-mediated neural dysfunction, and inflammation (immune dysregulation or proinflammatory cytokines).

Whether depression and cognitive impairment are associated with lupus activity or are a consequence of the stress of living with a chronic disease or are related to medications remains debatable. Nery et al[26] reported a significant positive correlation between depression severity (assessed using the Montgomery-Asberg Depression Rating Scale) and disease activity (SLEDAI score). In contrast, Jarpa et al[16] found no relationship between lupus activity and presence of a major depressive episode—or any other psychiatric diagnosis. In this larger study[16] (N = 87 [79 women]), which included Chilean patients, SLE activity did not correlate with psychological distress.

Our group found significant positive correlation between ADHD symptoms and disease activity (SLEDAI score) in a small cohort of mainly white women (20 of 22 patients).[25]

Genetics

Genetic predisposition is an important factor in the pathogenesis of SLE. Familial aggregation of lupus and a 40%–57% identical-twin concordance rate have been observed.[27] Nonidentical twins are usually discordant for clinical SLE, but unaffected siblings may have serologic abnormalities without clinical symptoms (1 in 3 twin pairs).[28] If a mother has SLE, her daughter's risk of developing the disease is 1:40, while her son's risk is 1:250.

Approximately 35 genes associated with lupus have been identified and either have been replicated or are near the threshold for genome-wide significance (eg, interleukin-1 receptor-associated kinase 1 [*IRAK1*]).[27] In a study by So et al,[29] heritability was calculated using 23 loci and was found to be 0.66, indicating that both genetic and environmental factors are important in the pathogenesis of SLE. There was a high frequency of human leukocyte antigen (HLA)-DR2 and HLA-DR3 (relative risk = 5.8) haplotypes and null complement alleles.

A recent case report[30] supports the role of ultraviolet light in the pathogenesis of SLE; sunlight can worsen rash, induce flare-ups, and precipitate neuropsychiatric symptoms in SLE.

Inflammation and Thrombosis

Inflammatory and thrombotic processes may lead to neuropsychiatric SLE, and differentiation between these processes is not always possible.[31]

Vasculopathy and coagulopathy result in decreased blood flow to the frontal and parietal lobe in neuropsychiatric SLE due to multifocal microinfarcts with or without evidence of thromboemboli. Microemboli from vegetations in lupus patients with Libman-Sacks endocarditis can lead to ischemic changes. Antiphospholipid antibodies predispose patients to thrombotic events. There is poor correlation between clinical, MRI, and neuropathological findings.[21]

Medications

The role of medications in the development of psychiatric symptoms in SLE is not clear and probably varies on a case-by-case basis, depending on dose and duration of treatment.

Steroids may down-regulate brain-derived neurotrophic factor (BDNF)[32] and cause depression, mania, psychosis, ADHD symptoms, headache, insomnia, and mood swings. Immune suppressants (eg, cyclophosphamide or azathioprine) may cause anemia, headache, fatigue, nausea, and cognitive impairment.[33] Mycophenolate mofetil can cause insomnia.[33] Opioids may cause fatigue, impaired attention, and worsening of depression.

A significant portion of patients (over 20%) present with depression, anxiety, or psychosis at the onset of SLE,[23] when steroids and immune suppressants have not yet been initiated. Psychosis usually improves with steroid treatment, as steroids are capable of restoring the blood-brain barrier. Distinct neuropsychiatric symptoms associated with lupus were described in the 19th century, when medications to treat SLE were not yet available.[34] On the basis of these observations, it is very likely that a significant portion of psychiatric symptoms are due to direct or indirect effects of SLE and are not caused by medications.

Psychiatric symptoms occur in half of SLE patients before diagnosis of their disease.[35] Only one-third of these patients seek professional help. According to Perry,[36] psychiatric symptoms associated with lupus rarely persist in isolation for more than 18 months; therefore, if the onset of the psychiatric disorder precedes diagnosis of lupus by more than 2 years, the psychiatric disorder should be considered as independent from the illness.

Because the literature about psychopathology and cognitive dysfunction in SLE is composed mainly of uncontrolled cross-sectional studies, more work is needed prior to drawing firm conclusions.

Stress

Psychiatric symptoms may also be influenced by disease-related psychosocial stressors. Being diagnosed with a chronic, serious, often fatal, recurring illness is a severe stressor that may cause intense anxiety or depression. Visible symptoms (eg, butterfly rash) may lead to social avoidance. Patients usually make efforts to conceal their symptoms from significant others, and, when these attempts fail, they become depressed. Depression severity is associated with perceived illness intrusiveness.[37] Fatigue and joint pain can lead to limited functioning, disability, and feelings of loss, inferiority, and inadequacy. Limited functioning may result in conflicts with significant others. Sleep deprivation is frequently present in lupus because of joint pain, anxiety, or depression and may result in fatigue and attention deficit. Anxiety is usually an early symptom—duration of illness is shorter in patients with anxiety disorder as compared to patients with other psychiatric symptoms.[38] Quality of the doctor-patient relationship is very important and can also influence severity of psychiatric symptoms.

There are conflicting data on the effect of psychosocial stress on the immune system.[39] It is unclear whether stress can precipitate flare-ups in lupus. Stress can cause worsening of psychiatric symptoms.[39]

Blood-Brain Barrier Dysfunction

A thrombosis or microembolus in brain microvessels results in local ischemia, oxidative stress, and opening of the blood-brain barrier. Epinephrine and activated serum matrix metalloproteinase 9 can also open the blood-brain barrier.[40] The blood-brain barrier dysfunction is usually transient and improves with steroids, but, without intervention, it may lead to increased leukocyte trafficking across the damaged endothelium potentiated by local cytokine release. Autoantibodies may cross the blood-brain barrier or be released intrathecally and cross-react with neuronal membrane proteins, resulting in permanent damage. According to the animal studies of Huerta et al,[40] the agent used to open the blood-brain barrier determines which brain region is made vulnerable to neurotoxic autoantibodies. For example, treatment with bacterial endotoxins (lipopolysaccharides) results in hippocampal neuron damage and memory deficit in mice immunized with a peptic mimetope of DNA. On the other hand, if mice are given epinephrine to open the blood-brain barrier, they lose neurons in the lateral amygdala and have deficient response in fear-conditioning paradigms. In contrast, autoantibodies against endothelial cells may result in diffuse blood-brain barrier damage.[40]

Autoantibodies

Over 20 autoantibodies are associated with neuropsychiatric SLE; however, specificity is lacking for any single neuropsychiatric manifestation with the exception of lupus psychosis.[41] Autoantibodies against endothelial cells may lead to microangiopathy in the central nervous system. Serum autoantibodies against endothelial cells may result in the breakdown of the blood-brain barrier, allowing the development of neurotoxic effects due to exogenous and endogenous substances (eg, hormones, drugs, medications, interferon-α).

Anti–double-stranded DNA (anti-dsDNA) antibodies cross-react with *N*-methyl-D-aspartate receptor subunits NR2A and NR2B in mice and humans[42] and signal neuronal death (apoptosis) through caspase-3–mediated pathways. Anti-dsDNA–positive patients are more likely to have renal involvement, and there is evidence that patients with renal dysfunction are more likely to develop psychiatric symptoms in lupus.[43] Antibodies against *N*-methyl-D-aspartate receptors (anti-NR2 antibodies) are associated with depression, psychosis, and hypomania, but not with cognitive dysfunction.[44]

Antiribosomal P glycoprotein autoantibodies were implicated in the pathogenesis of neuropsychiatric SLE. According to a recent meta-analysis by Karassa and colleagues,[45] the diagnostic value of serum antiribosomal P antibodies is negligible in neuropsychiatric SLE since these antibodies are present in one-third of patients with neuropsychiatric SLE, as well as in 15%–25% of patients without neuropsychiatric manifestations. In contrast, Hanly et al[46] recently found that antiribosomal P antibodies were associated with a future risk of lupus psychosis.

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It is unclear whether autoantibodies enter the central nervous system from the periphery after destruction of the blood-brain barrier or are released by B-cells intrathecally.

Cytokines and Chemokines

Cytokines and chemokines are also implicated in the pathogenesis of neuropsychiatric SLE. They may enter the CNS from the peripheral blood or be released in situ as a response to binding of antibodies to injured neurons.[47] Interferon-α causes microglial activation and inflammation in the central nervous system, leading to depression and psychosis. Increased levels of interleukin-6 and interleukin-8 were found in neuropsychiatric SLE.[48] Interleukin-6 levels were found to be increased in the cerebrospinal fluid without damage to the blood-brain barrier.[49]

Svenungsson et al[50] found elevated levels of messenger RNA for tumor necrosis factor–α, interferon-γ, and interleukin-10 in peripheral blood lymphocytes and elevated levels of interferon-γ and interleukin-10 in the cerebrospinal fluid of patients with neuropsychiatric SLE.

BIOMARKERS OF PSYCHIATRIC SYMPTOMS IN LUPUS

Immune dysregulation, characterized by immune activation of neuroglial cells, has been observed not only in SLE, but also in autism spectrum disorders, ADHD, and multiple sclerosis.[51] Serum autoantibodies against endothelial cells are common in SLE and autism spectrum disorders.[52] Antinuclear antibodies and increased cerebrospinal-fluid tumor necrosis factor–α levels are also observed in both SLE and autism spectrum disorders.[53]

Oxidative stress, mitochondrial dysfunction, and cerebral hypoperfusion were reported in SLE, autism spectrum disorders, ADHD, schizophrenia, Alzheimer's disease, dementia of human immunodeficiency virus infection, and Parkinson's disease.[54] Therefore, biomarkers of oxidative stress and mitochondrial dysfunction are not specific biomarkers of neuropsychiatric SLE or other psychiatric disorders.

In contrast, serum BDNF and interleukin-6 levels are promising serum biomarkers for psychiatric symptoms in SLE.[55] Ainiala et al[56] found increased serum matrix metalloproteinase–9 levels in SLE patients with neuropsychiatric manifestations and brain MRI abnormalities. The function of matrix metalloproteinase–9 (a zinc-containing endoproteinase) is to enhance T-cell migration through connective tissue.

Two proteins expressed by CNS astrocytes may serve as biomarkers of blood-brain barrier dysfunction: glial fibrillary acidic protein (GFAP) and S100β.[57] These proteins are not specific to blood-brain barrier dysfunction associated with lupus; primary and metastatic brain tumors, ischemia, hypertension, dementia, epilepsy, infection, multiple sclerosis, and trauma can increase levels of these proteins in the serum.

At present, there is no specific and sensitive biomarker for psychiatric symptoms in lupus.

IMMUNE DYSREGULATION IN OTHER PSYCHIATRIC DISORDERS

Schizophrenia

There is evidence of immune system overactivation in schizophrenia. Increased levels of serum interleukin-2 and interleukin-6 and decreased activation of lymphocytes have been observed in several studies.[58]

Several autoantibodies have been documented in schizophrenia, eg, anticardiolipin antibodies, antinuclear antibodies, and anti-DNA antibodies.[22] Removal of these antibodies using plasmapheresis is not effective in schizophrenia; however, patients with SLE who received plasmapheresis achieved long-term remission of psychosis without psychotropic medications.[22]

Depression and Anxiety

Proinflammatory cytokines (eg, interleukin-1β, interleukin-6, tumor necrosis factor–α, and interferon-α) and psychological stressors result in activation of the sympathetic nervous system (epinephrine and norepinephrine release) and the hypothalamic-pituitary-adrenal axis (corticotropin-releasing hormone, corticotropin, and cortisol release) and reduction of BDNF levels.[39]

Serum BDNF levels inversely correlate with clinical impairment and reduction of hippocampal volume in depression.[59] Antidepressant medications increase BDNF expression in the hippocampus and normalize serum BDNF levels.[32] Antidepressants reduce proinflammatory (eg, interleukin-6) and augment anti-inflammatory signaling in a subset of patients, possibly through regulatory effects on the sympathetic nervous system and hypothalamic-pituitary-adrenal axis.[60]

A large number of studies show that treatment of cancer and hepatitis C with interferon-α may lead to depression.[61] Interferon-α activates enzymes responsible for degradation of the serotonin precursor tryptophan (eg, indoleamine 2,3-dioxygenase; guanosine 5′-triphosphate cyclohydrolase I).[62] Selective serotonin reuptake inhibitors (eg, sertraline, citalopram) diminish the depressive symptoms provoked by interferon-α.[63]

On the basis of these findings, it seems that avoiding stress and treating anxiety and depression with antidepressants may improve outcomes in lupus. Controlled longitudinal studies are needed to prove this hypothesis.

Neurodegenerative Disorders

Patients treated with interferon-α develop not only depression, but also cognitive disturbances. Impaired concentration and memory, irritability, confusion, and disorientation were observed.[64] Interferon-α and other cytokines activate oxidative enzymes, and the metabolites of these reactions (eg, 3OH-kynurenine, quinolinic acid) may be neurotoxic through free-radical generation, causing neurodegeneration.

On the basis of these observations, neuroprotective medications may be effective in preventing cognitive

impairment in lupus. A recent 12-week placebo-controlled trial of memantine[65] among 51 patients failed to show improvement in cognitive performance. Neuroprotective medications might be effective for the prevention but not treatment of cognitive decline in lupus.

CONCLUSIONS

Depression and cognitive dysfunction are the most common psychiatric manifestations in SLE. Psychiatric symptoms occur in half of SLE patients before the diagnosis of their disease.[35] There is a great variation in the prevalence of psychiatric symptoms reported by published studies, which makes it difficult to compare findings. The main reason for this variability is the diversity of assessment methods. Only a limited number of studies used matched control groups. Most studies were cross-sectional in nature and reported the point prevalence only, not the lifetime prevalence of disorders. Medications and illness severity and duration were rarely taken into account. Controlled longitudinal studies are needed using standardized instruments to identify biomarkers associated with psychiatric symptoms in lupus.

Identification of lupus-specific biomarkers of cognitive impairment is a high priority. Discovering such biomarkers may guide prevention and treatment of serious psychiatric complications in SLE. There is a large (N = 1,047) ongoing prospective multicenter study being conducted by the Systemic Lupus International Collaborating Clinics that will follow patients for 10 years following diagnosis[46] to find associations between symptoms and serologic biomarkers. At present, we do not have specific and sensitive biomarkers of psychiatric symptoms in lupus, with the exception of the rare lupus psychosis, for which the antiribosomal P antibodies may have some predictive value.[46]

Attributing neuropsychiatric events to SLE, other potential causes (exclusions), and contributing factors (associations) is challenging, since we do not have specific and sensitive serum or imaging biomarkers of neuropsychiatric SLE. Hanly et al[46] developed 2 attribution models based on the ACR glossary for neuropsychiatric syndromes (based on onset, presence of concurrent non-SLE factors, and exclusion of "common" neuropsychiatric events such as headache, mild depression, mild cognitive impairment, and polyneuropathy without electrophysiologic confirmation). These models are helpful for the classification of neurologic and other physical symptoms, but they seem less applicable for the diagnosis of psychiatric disorders, for which biological, psychological, and social factors are taken into account simultaneously.

Unfortunately, the ACR definitions and diagnoses do not match current *DSM-IV* criteria. For example, "acute confusional state" does not exist in *DSM-IV*; this description seems to be identical with delirium due to a general medical condition. When a medical condition like SLE is present, on the basis of *DSM-IV* we cannot rule out that a certain symptom (eg, depression, anxiety, cognitive impairment) is related to the medical condition. In contrast, Hanly et al[46] concluded that all 52 cases of anxiety—and the majority of mood symptoms (78 of 132)—were due to "non-SLE causes." Bertsias and Boumpas[31] defined *primary neuropsychiatric SLE* (neuropsychiatric events that can be directly attributed to active disease) and *secondary neuropsychiatric SLE* (neuropsychiatric events that represent complications of the disease or its therapy or have causes unrelated to SLE, eg, infection or metabolic imbalance) and concluded that less than 40% of neuropsychiatric events could be directly attributed to SLE. This study[31] included both neurologic and psychiatric symptoms; therefore, the association between lupus severity and psychiatric symptom severity cannot be ruled out. Some studies show that depression[66] and attention deficits[25] might be associated with lupus severity. Jarpa et al[16] did not find an association between psychiatric symptoms and disease activity.

Because the literature about psychopathology and cognitive dysfunction in SLE comprises mainly uncontrolled studies, more work is need prior to drawing firm conclusions. In female patients with new-onset depression, cognitive dysfunction, or psychosis *and* a family history of SLE, a detailed medical history, physical examination, and determination of antinuclear antibody titer might help clinicians to raise the possibility of lupus. The diagnosis will need to be confirmed by further laboratory tests.

Evidence-based data are scarce regarding treatment of psychiatric symptoms in SLE. Treatment of depression, anxiety, psychosis, and cognitive impairment in lupus remains empirical at present. We do not know which antidepressants and antipsychotics work best in lupus. The European League Against Rheumatism guidelines[67] recommend treating depression in lupus the same way as in non-SLE patients. Controlled clinical pharmacotherapy trials are needed to develop evidence-based guidelines for the treatment of psychiatric symptoms in SLE. Our current diagnostic criteria, disease severity indicators, and diagnostic methods also need improvement.

The pathogenesis of neuropsychiatric SLE is a complex 3- or 4-step process. These processes are fluctuating; they are interrelated and are modified by treatment interventions. Environmental insults are detectable on the molecular level (mitochondrial dysfunction), cellular level (neuronal damage), or organ level (eg, vasculopathy/coagulopathy, blood-brain barrier dysfunction).

Clarification of the pathogenesis of psychiatric symptoms in SLE may provide insights into the neuroimmune pathogenesis of psychiatric symptoms in other psychiatric disorders, eg, schizophrenia, depression, anxiety, attention deficit, and dementia. Autoantibodies, microglial activation, oxidative stress, mitochondrial dysfunction, blood-brain barrier dysfunction, and cerebral hypoperfusion are frequently observed processes in these disorders. Immune suppression, plasmapheresis, and anti-inflammatory drugs may be effective in a subset of patients with psychiatric disorders who carry biomarkers of autoimmune processes.

In summary, further controlled longitudinal studies are needed to clarify the pathogenesis of psychiatric symptoms in SLE and to develop guidelines for the diagnosis, prevention, and treatment of these often overlooked symptoms.

Drug names: azathioprine (Azasan, Imuran, and others), citalopram (Celexa and others), cyclophosphamide (Cytoxan and others), memantine (Namenda), mycophenolate mofetil (CellCept and others), sertraline (Zoloft and others).

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