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REVIEW

Depression in systemic lupus erythematosus: a systematic review

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ABSTRACT

Depression is the most common psychological symptom in patients with systemic lupus erythematosus (SLE). A large fraction of these patients remains undiagnosed due to subclinical presentation or is missed in the routine workup of SLE. Many factors have been reported in the literature which can be used as predictor of depression in SLE. Lupus patients also have higher risk of suicidal tendencies than the general population. Pathogenesis of depression in SLE is multifactorial and involves complex interactions between cytokines, antibodies, genetic factors, etc. Approach to such patients consists of studies that establish diagnosis of SLE, distinguish between organic and functional etiologies, and exclude symptoms not due to SLE. Various hematological, cerebrospinal fluid investigations, electroencephalography, psychometric testing, as well as neuroimaging modalities are involved in diagnostic workup of lupus patients with depression. Patients with only psychological causes for depression are treated with antidepressants. While in case of organic disease, one treats with glucocorticoids, immunosuppressants, and antidepressants. Electroconvulsive therapy can be considered in very severe cases not responding to maximum therapy.

Key words: Antidepressants, depression, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder with multi-organ involvement, predominantly seen in females and with a relapsing-remitting course [1]. Its most common manifestations are arthritis, cutaneous lesions, renal disease, and neuropsychiatric symptoms [1].

One of the presentations of SLE is central nervous system (CNS) involvement. CNS involvement in SLE or lupus can be in a wide spectrum of clinical presentations such as mood disorders, anxiety, and cerebrovascular accidents [2]. The first description of mental changes in lupus was reported by Kaposi in 1872 [3]. Since then, a lot of research has been done into this topic, but still CNS involvement in lupus is largely unrecognized and misunderstood [4].

The first attempt towards classification and nomenclature of nervous system disorders in lupus was done in 1979 by Kassan and Lockshin [5]. Later in 1999, the American College of Rheumatology (ACR) developed a nomenclature system for 19 neuropsychiatric syndromes in SLE: neuropsychiatric SLE (NPSLE) [2]. Case definitions including diagnostic criteria, important exclusions, and methods of ascertainment were developed for 19 NPSLE syndromes.

Depression is the most common psychological symptom in patients with lupus [6]. It falls under the case definition of mood disorders in ACR classification [2]. Detailed diagnostic criteria for mood disorders in SLE was given by ACR [7]. Several studies that have looked into the prevalence of depression in lupus patients have reported point prevalence rate in the range of 11–65.8% [Table 1] [8-24]. This wide variation may be due to difference in the epidemiology of various sample populations as well as variations in the diagnostic methods employed by various groups. In one of the studies, lifetime prevalence of depression in SLE was reported to be 69% [25].

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Risk Factors

Depression by itself is an excellent example of the iceberg phenomenon. There is slow progression from subclinical depression to clinically significant disease. For every case of depression in SLE diagnosed, there are many more which are subclinical or are missed in the routine workup of lupus. Many cases remain undiagnosed due to delay and hesitancy in seeking medical care [17,26]. In a significant number of cases, depression may be present when patient is diagnosed of lupus [26].

Many factors which can be used as predictors of depression in lupus have been reported in the literature. Most important ones are appearance concerns, inadequate pain control, illness intrusiveness, perceived severity of disease, concealment of symptoms, and major life events [27-30]. Depression is more likely in the setting of poor quality of medical care [28]. Diabetes mellitus, vascular disease, unemployment, and lower levels of education are also found to be associated with depression in isolated studies [18,22,23,31].

A significant proportion of these cases also has suicidal tendencies. SLE patients are at five times higher risk of

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Table 1: Studies describing prevalence of depression in systemic lupus erythematosus patients

Author	Year of publication	Diagnostic method	*n*	Point prevalence %
Miguel et. al.[8]	1994	HAM-D	43	44
Ainiala et. al.[9]	2001	Beck Depression Inventory	46	39
Brey et. al.[10]	2002	SCIDs-I, Calgary Depression Scale	128	28
Hanly et. al.[11]	2005	HADS	53	11
Lapteva et. al.[12]	2006	Beck Depression Inventory II	60	31
Harrison et. al.[13]	2006	Center for Epidemiological Studies Depression Scale	93	16
Waheed et. al.[14]	2006	Aga Khan University Anxiety and Depression Score	111	65.8
Bachen et. al.[15]	2009	Composite international Diagnostic interview/DSM IV criteria	326	47
Petri et. al.[16]	2010	Calgary Depression Scale	111	31
Julian et. al.[17]	2011	Center for Epidemiological Studies Depression Scale	150	26
Julian et. al.[18]	2011	Center for Epidemiological Studies Depression Scale	663	17
Jarpa et. al.[19]	2011	Mini-International Neuropsychiatric Interview - Plus, HADSs	83	22
Karol et. al.[20]	2013	Beck Depression Inventory II	127	41.7
Sehlo and Bahlas[21]	2013	SCID-I - Clinical Version; HADS - Depression subscale	80	18.75
Maneeton et. al.[22]	2013	HAM-D17	62	45.2
van Exel et. al.[23]	2013	Beck Depression inventory	102	16.6
Shen et. al.[24]	2013	Self-Rating Depression Scale	170	32.9

HAM-D: Hamilton Depression Rating Scale, SCID-I: Structured clinical interview for DSM-IV Axis I Disorder, HADS: Hospital Anxiety and Depression Scale

having suicidal tendencies [32]. Suicidal thoughts are present in around 10–12% of SLE patients [19,33]. Psychosis, insomnia, history of photosensitivity, incompletely controlled disease, tapering corticosteroids dose, major life events in the preceding month, previous suicide attempt, diffuse slowing on electroencephalogram, and presence of hypocomplementemia are risk factors for attempting suicide in SLE [33,34].

Pathogenesis

Pathogenesis of depression in lupus is highly debated and is not clearly understood. There are mainly two theories which are put forth as an explanation for the pathogenesis of depression. First theory states that depression in SLE is due to psychosocial factors due to the stress of being diagnosed with a chronic disease at a very young age. Some of the studies support this theory [6,35,36] while others have failed to establish any significant association between depression and psychosocial factors [37]. Other theory suggests that depression in lupus patients is due to organic damage taking place in the CNS. This damage is most likely thought to be immune mediated. Here, as well, there are studies which support this hypothesis [18,30,38]. On the other hand, some investigators disagree to this proposal [19,23,36].

Various autoantibodies have been investigated to determine if they are pathogenic for depression. Some investigators believe that a strong association exists between the occurrence of neuropsychiatric symptoms and the presence of antineuronal and other antibodies [39]. Antiribosomal P antibody is believed to have strong association with depression in SLE in some [40,41] but not most studies [42,43]. A few studies have also suggested an association between antibodies against human N-methyl-D-aspartate receptor types (anti-NR2 antibodies) and depressed mood [12,44]. However, other studies have not confirmed these observations [13]. Antiganglioside (aGM1-IgM) [45] and antiendothelial cell antibodies [39] are also reported to have association with depression. However, these findings need to be confirmed in larger controlled studies.

Proinflammatory cytokines released from monocytes/macrophages (tumor necrosis factor-alpha [TNF-α], interleukin-1 beta [IL-1β], IL-1, IL-6, IL-8, etc.,) may play an important role in the development of depression in lupus patients [46,47]. Blood–brain barrier disruption is an essential component of NPSLE pathogenesis [48]. TNF-α, TNF-like weak inducer of apoptosis (TWEAK) may play important role in this process [46,49]. Once blood–brain barrier is compromised, other autoantibodies may gain access to intrathecal space.

Depression in SLE patients is also reported to be associated with central blood flow reductions in discrete temporal and frontal regions [50]. It is not clearly understood if this reduction in central blood flow is caused by cytokines/autoantibodies/or some other unknown factor.

Depression can also be caused by treatment with corticosteroids through downregulation of the brain-derived neurotrophic factor [51]. The role of various environmental factors

(retrovirus, ultraviolet light, stress, medicines) can also not be ruled out [4,52].

Hereditary predisposition can also be present in lupus patients for developing depression [53,54]. Link polymorphism of serotonin transporter gene promoter region (PR-5HHT) is associated with depression in lupus patients [55].

To sum up, pathogenesis of depression cannot be explained on the basis of a single theory/mechanism. Mechanism for this disease is essentially multifactorial, which involves complex interactions between cytokines, antibodies, genetic factors, and environmental factors. Multifactorial pathogenesis of depression in SLE is described in Figure 1.

Diagnosis

Diagnostic tests that establish a specific diagnosis of neuropsychiatric lupus do not exist. Approach to a patient with neuropsychiatric symptoms consists of studies that establish diagnosis of SLE, distinguish between organic and functional etiologies, and exclude symptoms not due to SLE [56].

Careful history and physical examination should be done with special emphasis to look for depressive mental state/suicidal thoughts. A large proportion of these cases does not seek medical care for their depression [26]. Primary care doctors/ rheumatologists taking care of the patients must be proactive to pick up the disease early. These patients often have treatment

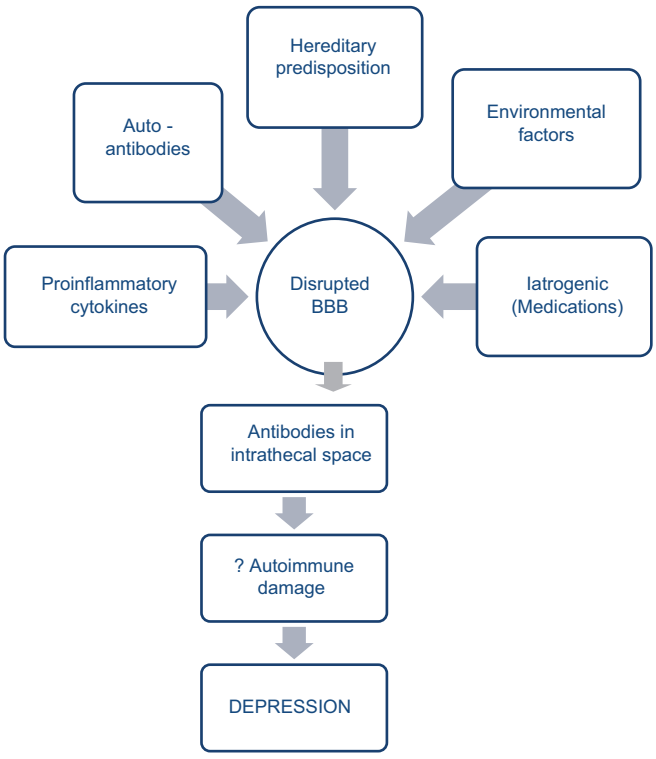

Figure 1 Pathogenesis of depression in systemic lupus erythematosus

adherence problems [57]. So any treatment plan should be ensured through strict follow-up.

Initial evaluation of SLE patient with (new) signs or symptoms suggestive of neuropsychiatric disease is comparable to that in non-SLE patient with the same manifestation to rule out secondary causes such as infections, metabolic, endocrine, and adverse drug reaction [58]. ACR has provided guidelines for diagnostic workup of patients with NPSLE [2,59]. A battery of hematological, cerebrospinal fluid (CSF) investigations, electroencephalography (EEG), psychometric testing, as well as neuroimaging modalities are involved in diagnostic workup of lupus patients with depression [56,59].

These tests are divided into two categories. First one involves investigations which should be done in routine while other is investigational which is done in special conditions to rule out other differentials. Important part of this diagnostic workup is to exclude other systemic illnesses and medications which might be confounding with the diagnosis of NPSLE. Psychometric testing can be used in setting of depression to rule out organic from psychosocial disease [56]. Recommendations for laboratory evaluation and diagnostic imaging in SLE patients with depressive symptoms are summarized in Table 2.

Neuroimaging is reserved for refractory cases who do not respond to initial treatment of depression. Magnetic resonance imaging (MRI) is the gold standard for neuroimaging in NPSLE [60]. If MRI is not available, computed tomography can be done [55]. European League Against Rheumatism (EULAR) recommends that MRI protocol (brain and spinal cord) should include conventional MRI sequences (T1/T2, fluid attenuated inverse recovery, diffusion-weighted imaging) and gadolinium-enhanced T1 sequences [61].

ACR recommends the use of Center for Epidemiological Studies - Depression Scale for evaluation of depression in NPSLE patients [62].

Management

The management of depression in SLE depends on whether the physician thinks that the depression has a neurological basis (inflammation of the brain, a stroke, seizure, perhaps the presence of autoantibodies, elevated cytokines) versus a psychological cause(where signs of neurological basis are absent). One can differentiate neurological from psychological causes by imaging (MRI), EEG, CSF analysis, and psychometric testing [56]. Patients with only psychological causes are treated with antidepressants while in case of organic disease, one treats with glucocorticoids, immunosuppressants, and antidepressants [61].

At present, there is a paucity of published controlled trials for treatment of depression in SLE patients [60]. In a study, combination of celecoxib (anti-inflammatory) and

Table 2: Laboratory evaluation and diagnostic imaging in neuropsychiatric systemic lupus erythematosus

Routine	Investigational
Blood	Autoantibodies
Complete blood count including platelets and peripheral smear examination	Antineuronal antibodies
Creatinine/creatinine clearance	Antiribosomal P
Urinalysis	Antilymphocyte
Liver function test	Antiglycolipid
Electrolytes	Antineurofilament
C3, C4, or CH50	Antiglial
Anti - double stranded DNA	Antiganglioside
Erythrocyte sedimentation rate or C - reactive protein	Antisphingomylein
Antiphospholipid antibodies	Antigalactocerebroside
Lipid profile, glucose	Tests for hypercoagulability
	Factor V Leydin
	Factor XII
	Protein C or S
	Homocysteine
	Soluble cytokines
Cerebrospinal fluid	Antineuronal antibodies
Cell count	Antiribosomal P
Protein	Myelin basic protein
Glucose	Soluble cytokines
Cultures	Complements
Gram stains and other special stains	
Venereal Disease Research Laboratory	
IgG index	
Oligoclonal bands	
Imaging	Diffusion and perfusion MRI
MRI or CT	MRI spectroscopy
	Single-photon emission CT
	Positron emission tomography
Encephalography	
Psychometric testing	

MRI: Magnetic Resonance Imaging, CT: Computed Tomography

fluoxetine (antidepressant) has been reported to have greater antidepressant effect than fluoxetine alone [63]. EULAR recommends treatment of depression in SLE patients with a combination therapy of glucocorticoids, immunosuppressant, and antidepressant [60].

Electroconvulsive therapy (ECT) can be used in very severe cases who do not respond to the maximum therapy. There is a case series of three patients in which SLE patients with psychosis were treated successfully with ECT, but there is no study or case report describing use of ECT in SLE-associated depression [64].

Most of these SLE patients with depression recover within a year with the help of social support along with medical care [65]. Other patients may incorporate depression into their personality, thereby developing psycho(somatic) complaints such as insomnia, anorexia, constipation, myalgia, and arthralgia [65]. Many of these patients develop chronic fatigue syndrome [23,66]. Patients may also develop "psychotic features" with increasing despair, loss of hope, and even suicidal tendencies [65]. It is recommended that such patients should be managed in psychiatric facilities. Psychological interventions are found to be efficient in the management of depression in SLE [67].

Discussion

Various theories have been suggested in the literature to explain pathogenesis of depression in SLE. Actual mechanism is more likely to be multifactorial with complex interaction of various variables. Figure 2 also explains relation between stress and depression forming cyclic sequence of events. It is very difficult to determine starting point of this cycle. Health-related quality of life in these patients is affected by fatigue, disease activity, and psychiatric disease [68,69]. There is very little literature which describes diagnostic workup and management of depression in SLE. Most of the guidelines available are for NPSLE which is a broader aspect of this disease. In a patient who presents with depression, only a few specific investigations are required out of the whole battery of investigations recommended by ACR. Treatment of such cases is with a combination of glucocorticoids, immunosuppressants, and antidepressants.

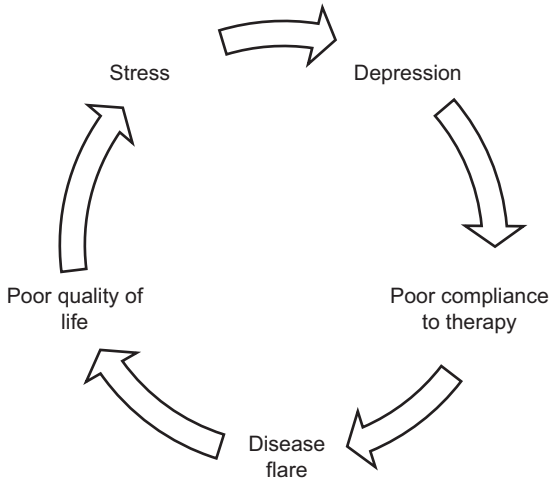

Figure 2 Relation between disease stress and depression

Conclusion

Depression is the most common psychiatric presentation of SLE. A large proportion of these cases still remains undetected. Suicidal thoughts are very common in such patients. Numerous red flag signs have been described in the literature to suspect such events. Finally, primary objective of patient care in this setting is to improve quality of life for the patients. Better control of disease activity, psychiatry disease, and stringent pain control can help in ensuring better quality of life for patients.

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