DEPRESSION - A FELLOW TRAVELER WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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(Abstract): Systemic lupus erythematosus (SLE) is a chronic multisystem inflammatory disorder that occurs primarily in women of childbearing age, immunologic abnormalities being a prominent feature of the disease. Psychiatric disorders frequently coexist, depression being the most common mood disorder in neuropsychiatric lupus. This literature review was performed through searching MEDLINE database for full-text English-language articles - original research, systematic review and updates published in the last five years (2010-2015), using the keywords “depression and systemic lupus erythematosus”. The main outcomes identified were prevalence and predictors of depression in various cultural and ethnic groups, depression-related clinical issues (suicidal ideation, cognitive impairment, altered body image, sleep and sexual disturbances, influence of SLE treatment), and influence on quality of life. A multidisciplinary approach that takes into account the polymorphism and individual variability of the SLE clinical manifestations helps to improve early detection of depression, which is responsible for the increased risk of comorbidities, suicidal attempts, decreased treatment adherence, and impaired quality of life. Physicians across all specialties involved in the care for lupus patients should be aware of the major prevalence of this condition, while helping patients to cope with their disabling disease. Keywords: DEPRESSION, SYSTEMIC LUPUS ERYTHEMATOSUS, NEUROPSYCHIATRIC LUPUS.

Systemic lupus erythematosus (SLE) is a chronic multisystem inflammatory disorder that occurs primarily in women of childbearing age, immunologic abnormalities being a prominent feature of the disease. Diagnosis is based on clinical and immunological criteria as defined by the 1997 American College of Rheumatology (ACR) and the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria (1). The course of the disease is chronic, relapsing, and unpredictable, with flares and remissions that may last for years. Medication used to treat SLE depends on the severity of the disease and clinical manifestations, including biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs),
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corticosteroids and nonsteroidal anti-inflammatory drugs, and antimalarials (2).

In chronic somatic diseases, like SLE, psychiatric disorders frequently coexist, patients having increased level of worry and concern about their condition, the psychological disturbances negatively affecting their emotional status and quality of life and leading eventually to increased risk for disability and death (3, 4). Patients with lupus suffering from one or more neuropsychiatric symptoms, such as cognitive impairment, anxiety, depression, mood disorder, psychosis, represent a clinical category named “neuropsychiatric lupus” (NPL), which includes a broad spectrum of conditions, 12 central nervous system and 7 peripheral nervous system – related, according to the 1999 American College of Rheumatology recommendations (5). These can result in increased severity, refractoriness to medical treatment and marked functional impairment (6).

**DEPRESSION AS PART OF THE NEUROPSYCHIATRIC LUPUS**

Understanding of neuropsychiatric lupus is still limited, but several pathogenic pathways were identified, some of them related to depression (5, 7) (tab. I).

### TABLE I

<table>
<thead>
<tr>
<th>Pathogenic pathway</th>
<th>Clinical relevance</th>
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<tbody>
<tr>
<td><strong>Vasculopathy</strong></td>
<td>small vessel thrombotic-vasculopathy in brains of NPL patients</td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
<td>➢ anti-ribosomal-P - lead to neuronal apoptosis</td>
</tr>
<tr>
<td></td>
<td>➢ anti-DNA/NR2 - neuronal apoptosis, hippocampal neuron damage coupled with memory loss</td>
</tr>
<tr>
<td></td>
<td>➢ anti-DNA 16-6 idiotype - correlate with disease activity, cause histological changes in the hippocampus and amygdale, affecting behavioral and cognitive functions in mice</td>
</tr>
<tr>
<td></td>
<td>➢ anti-phospholipid/anticardiolipin - activation of coagulation pathways, predisposing to focal neurological manifestations (stroke, transverse myelitis, chorea), seizures, migraine, and cognitive impairments</td>
</tr>
<tr>
<td></td>
<td>➢ anti-GABA - high levels in cerebrospinal fluid</td>
</tr>
<tr>
<td><strong>Blood brain barrier disruption</strong></td>
<td>enable auto-antibodies to penetrate the brain and cause their pathogenic effects, further inducing the production of pro-inflammatory cytokines (anti-ribosomal-P, anti-NR2 antibodies)</td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td>IL-2, IL-10, interferon (IFN)-α, IFN-γ elevated in serum and cerebrospinal fluid</td>
</tr>
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</table>

Depression is the most common mood disorder in neuropsychiatric lupus, having a lifetime prevalence of up to 65% in SLE patients. An association of depression and specific antibodies directed at ribosomal-P, N-methyl-D-aspartate (NMDA) receptor, and other neuronal epitopes has been suggested (5, 8).

Symptoms of clinical depression in lupus are lack of energy, diminished sexual appetite, sleep disturbances, modified eating pattern, and fatigue (3, 9) that could be attributed to both conditions – SLE and depression. Sometimes clinical depression is a symptom of neuropsychiatric lupus, as a result of the complex interplay of biochemical abnormalities affecting the brain, but other times depression comes later in the course of disease, as a result of patient response to the burden of disease, social
consequences, and symptoms severity, leading to feelings of sadness, helplessness and rejection, both instances being part of a comprehensive approach to depression in SLE (10).

Physicians usually use the SLE Disease Activity Index (SLEDAI) to determine the level of disease activity and whether the flare is mild, moderate, or severe; but depression is not one of the specific symptoms on SLEDAI, needing other type of workup to determine it, and that might be a reason for overlooking this diagnosis and related-issues, even though they have a great impact on quality of life and the course of disease (11, 12). The importance of early identification of neuropsychiatric involvement in SLE, when symptoms could be mild, required the development and validation of simple clinical screening tools, such as physician-administered or self-reported standardized questionnaires. This assessment is challenging and there is need for validation in large cohort studies, cross-culturally adapted (6, 13).

This literature review was performed through searching MEDLINE database for full-text English-language articles - original research, systematic review and updates, published in the last five years (2010-2015), using the keywords “depression and systemic lupus erythematosus”. The research initially identified 429 articles and excluded studies on topics involving cutaneous lupus erythematosus without systemic involvement, drug-induced lupus erythematosus, and pediatric age; a number of 30 articles were retained. The main outcomes related to depression in SLE patients were prevalence and predictors of depression in various cultural and ethnic groups, clinical issues depression-related (suicidal ideation, cognitive impairment, altered body image, sleep and sexual disturbances, influence of SLE treatment), influence on quality of life.

DEPRESSION IN LUPUS – PREVALENCE DATA AND PREDICTORS AROUND THE WORLD

There are many studies conducted all over the world to help identifying the symptoms and particular appearance of depression related to local culture and religious beliefs. In some geographical areas, depression may be underrated and patients do not receive the proper treatment.

In a recent study on European population, the prevalence of depression in SLE subjects is 16.6% compared to 6.7% in the general population (P < 0.001), as resulted from the ODIN study (Outcome in Depression International Network) and it is not related to disease activity or organ damage (14).

In Asia, a Chinese cross-sectional study (15) investigated the relationship between disease parameters, quality of life, and psychological status in patients with SLE. It included 170 patients with SLE and 210 healthy individuals matched for age, gender, education, and work status. This study revealed that 20.3% of SLE patients were diagnosed with anxiety and 32.9% with depression, significantly higher than healthy people. Severe disease status, higher disease activity and lower quality of life significantly correlated with depression and anxiety in the Chinese SLE patients. Risk factors included poorer coping styles, ongoing life events, exposure to stress, and low social support. Impaired mental health and pain were the most powerful predictors of anxiety and depression in this study. A cross-sectional study conducted in Thailand on 62 SLE patients identified the presence...
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of depression in 45.2% and anxiety in 37.1% of the patients. It also concluded that higher anxiety score (HAM-A score) and younger age were significant predictors of depression in SLE (16). In addition, a retrospective study in Saudi Arabia found 15.2% SLE patients with depression and 17.4% with signs of psychosis (17).

In South America, a Chilean study examined 83 patients with SLE for common mental disorders, psychological sufferance, disease activity (SLEDAI), and biological determinants. A major depressive episode was the most frequent diagnosis (21.7%), suicidal ideation was present in 9.6%, but there was no association with disease activity and anti-ribosomal P antibodies (18).

A major longitudinal study enrolling 1609 North-American SLE patients in the Hopkins Lupus Cohort aimed at identifying the predictors of depression in lupus. The trial demonstrated an incidence of depression of 29.7 episodes per 1000 person-years and found several independent predictors of depression in lupus: recent diagnosis, non-Asian ethnicity, myelitis, cutaneous activity, disability, and higher-dose prednisone (>20 mg daily) (19). In another cross-sectional study that used structured clinical interview techniques for diagnosing depression, major depressive disorder was the most prevalent disorder (17%), followed by minor depression (6%) and dysthymia (4%) (20).

DEPRESSION-RELATED CLINICAL ISSUES

Sleep and sexual disturbances. Sleep (insomnia, hypersomnia) and sexual disturbances are common in patients coping with chronic disease, lupus included. An Italian clinical trial compared 81 female SLE patients with 53 hypertensive female patients as controls regarding the sleep pattern. The collected data showed a 2.5 times higher probability of poor sleep quality in SLE patients compared to the hypertensive ones. Depressive symptoms were significantly associated with sleep disturbances in SLE, but not with the activity or duration of the disease (21). These findings suggest that depression might be responsible for poor sleep quality in SLE.

Sexual function in women with SLE was analyzed in a cross-sectional, case-control study including 65 lupus patients and 55 healthy subjects. Women with SLE reported significantly impaired sexual function, associated with somatization, obsessive-compulsive behavior, depression and paranoid ideation; multivariate analysis indicated that depression, vitality and Positive Score Discomfort Index (PSDI) were significantly associated with low sexual function, eventually affecting the quality of life (22).

Suicidal ideation. It is of major importance to evaluate the patients diagnosed with depression and SLE for suicidal ideation, in order to prevent fatal events. A study conducted in Iran (23), which included 85 SLE patients, concluded that 60% of the patients had depression, the most common depressive symptoms being fatigue (88%), irritability (82%), sadness (77%), and somatic preoccupation (76%). The least common symptoms of depression were weight loss (34%), low energy level (28%), and suicidal ideation (10%). In a larger Chinese study, including 285 patients, 34% had current suicidal ideation. The individual risk factors found by the researchers were religious beliefs, financial problems, duration of SLE, poor family functioning, and negative coping style (24).

Cognitive impairment associated to depression. Patients presenting with de-
pression and SLE have to be screened for cognitive impairment because they seem to be more exposed (9) and it may have a deleterious influence on the evolution of the disease and course of treatment. In addition, it seems that SLE patients with cognitive dysfunction have higher titers of auto-antibodies also linked to depression, such as anti-ribosomal-P, anti-N-methyl-D-aspartate (NMDA) glutamate receptor (5, 8). It is known that cognitive impairment is present in 80% of SLE patients ten years after diagnosis, but it could exists even in early stages, related to depression. A multicenter cohort study included 111 patients newly diagnosed with SLE who underwent depression and cognitive function testing, the results showing that depressed lupus patients had poorer cognitive performance. Treatment for depression might improve cognitive functioning in these patients, but further studies are needed (25).

**Body image.** Body image is also affected in chronic disabling disease with significant cutaneous and musculoskeletal involvement like lupus. Studies showed that body image quality of life inventory (BIIQLI) scores were significantly worse in SLE patients than in non-SLE patients, being correlated with self-reported depression and overall damage (26). Education, cognitive behavioral therapy, and cosmetic training lead to improved measures of body image, psychological well-being, and quality of life, showing that altered body image is modifiable in SLE (27).

**Associated clinical conditions in SLE patients with depression.** From the clinical picture of SLE, lupus arthritis seems to be related to depression. A cohort study of 127 lupus patients identified moderate or severe depressive symptoms in 41.7% of patients, the most significant variable associated with these symptoms being pain from lupus arthritis (28). A Spanish study including 84 SLE patients aimed to determine the possible relationship between fibromyalgia and psychiatric disorders in SLE. First of all, it identified fibromyalgia in 35.7% of the SLE patients, depressive symptoms in 19% and anxiety in 35.7%. The authors concluded that there is a high prevalence of fibromyalgia in SLE patients and a strong association with depressive and anxiety symptoms (P<0.001), but little or no impact of disease activity on psychiatric symptoms (29).

**Influence of immune response.** In this respect, there are conflicting results: some trials revealed that cerebro-reactive autoantibodies present in the cerebrospinal fluid (anti-N-methyl-D-aspartate and anti-ribosomal P) can cause significant damage to brain neurons (including the amygdala), potentially leading to depressive symptoms (5, 8) while others did not demonstrate a significant association between anti-ribosomal P antibodies and depression in SLE (18). The potential role of pro-inflammatory cytokines in developing depression and poorer quality of life is still unclear. A case-control study conducted in Singapore revealed that higher serum tumor necrosis factor-alpha levels are significantly associated with more severe depressive symptoms and decreased quality of life as assessed by SF-36, in patients with SLE (30).

**Influence of SLE treatment.** Medication is critically important in the therapeutic approach of SLE but many drugs have side effects that include depression. Glucocorticoids are widely used but they display severe side effects after prolonged use, such as hypertension, dyslipidemia, diabetes, behavioral changes, immunosuppression, memory impairment, mood disturb-
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Depression, gastrointestinal bleeding, glaucoma and cataract, osteoporosis.

It is necessary to strictly assess the patients prior to prescribing this drug, especially in larger doses (> 20 mg daily), in order to maintain the lowest necessary dose to achieve therapeutic effects, even though it is not clearly defined that corticosteroids are exclusively responsible for the appearance of major depressive disorder in patients with SLE. One study on 57 female patients with SLE found that of these up to 80% were treated with at least one corticosteroid and a large number of them presented emotional disturbances, such as depressive state, that coincided with the prolonged use (31) while another prospective longitudinal study (32) highlighted the importance of psychiatric examination prior to prescribing corticosteroid therapy because of the early onset of depression and anxiety during the first week of treatment. Risk factors were higher doses and prior history of psychiatric disorders, underly the need to identify patients at risk, because up to 22% of the patients with depression and corticosteroid treatment develop a severe form of disease, with suicide attempts (33). So far, there is no particular medication that had been shown specific for treating depression associated with SLE.

Quality of life in patients with SLE and depression. Systemic lupus erythematosus is a long-term complex disorder also affecting social functioning. When assessing patients with SLE it is important to take into account the influence of depression on patients’ quality of life. In patients in the PATROL study (Patients Reported Outcomes in Lupus), namely 125 Caucasian and Hispanic lupus patients, quality of life assessment was done using the Short Form-36 (SF-36) questionnaire. Depression, and not disease activity as measured by SLEDAI, significantly correlated (p<0.0001) with the majority of SF-36 domains, and appeared to have a major impact on quality of life in both ethnic groups with SLE (33).

Major contributors to decreased quality of life in lupus include fatigue, fibromyalgia, depression, cognitive dysfunction, altered body image, sleep and sexual dysfunction, but these are not related to disease activity (22, 26, 34). A meta-analysis including six randomized controlled trials comprising 394 participants and conducted by Chinese researchers concluded that psychological interventions (cognitive-behavioral therapy) significantly reduced the degree of depression (standard mean difference = −0.44, 95% [CI]: −0.78–0.10; P = 0.01), improving the quality of life, even if there was no effect on pain, disease activity, fatigue or mental health (4).

In the absence of large epidemiological studies and SLE databases there are multiple areas of “unmet need” in these patients, including firstly delayed diagnosis, depression/anxiety symptoms, sleep disturbances, and poorer quality of life, as a recent Australian systematic review has shown (35).

CONCLUSIONS

Given the polymorphism and individual variability of the SLE clinical manifestations we believe that the multidisciplinary approach could help improve early detection of depression, which is responsible for the increased risk of comorbidities, suicidal attempts, decreased treatment adherence, and impaired quality of life. Based on the available research data, physicians across all specialties involved in caring lupus patients should be aware of the major prevalence of
this condition, while helping patients to cope with their disabling disease. Patients with systemic lupus erythematosus should be permanently encouraged, right from the time of diagnosis, to build-up a personal strategy of defense against depression, through physical activity, psychological counseling, cognitive behavioral therapy, and social exercise, in addition to the pharmacological approach when needed.

REFERENCES

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