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Review

Psychiatric and neuropsychological manifestations of systemic lupus erythematosus

Pierluigi Fietta[1], *Pieranna Fietta*[2], *Giovanni Delsante*[2]

[1] Department of Psychiatry, Hospital of Lodi, Lodi, Italy; [2] Unit of Internal Medicine and Rheumatology, University Hospital of Parma, Parma, Italy

Abstract. *Background and aim*: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease which may involve any organ and system, including peripheral, autonomic, and central nervous system (CNS). According to the American College of Rheumatology nomenclature, the term "neuropsychiatric SLE" identifies neurological and psychiatric syndromes occurring in patients at any time, not attributable to other causes, and categorized in three main groups, namely neurological syndromes of CNS, neurological syndromes of peripheral nervous system, and diffuse psychiatric/neuropsychological syndromes. The SLE neurological and psychiatric manifestations are usually reported together, and specific data on SLE psychopathology are limited. We aimed to electively focus on prevalence, pathogenesis, diagnostic aspects, and current therapeutic options of diffuse psychiatric/neuropsychological SLE syndromes in adult and pediatric patients. *Methods:* A detailed search of concerning literature was performed in PubMed (U.S. National Library of Medicine) database. *Results*: In both adulthood and childhood, psychiatric/neuropsychological syndromes are frequent and challenging SLE manifestations, whose prevalence is likely underestimated, owing to systematic assessment is not routinely performed in patients. Ischemia (due to disease-related vascular injury or cerebral vasospasm) and inflammatory/immunopathologic mechanisms appear to be the main pathogenic factors. Standardized treatment guidelines are not presently available, however, therapeutic recommendations have been proposed. *Conclusions*: Due to the high prevalence and significant suicidality risk of SLE psychiatric syndromes, systematic assessment to provide prompt diagnosis and adequate care should be critical part of SLE patients' evaluation protocol, and universally accepted and validated evaluating tools should be performed and introduced in the clinical practice, as well as widely experienced therapeutic strategies. (www.actabiomedica.it)

Key words: neuropsychiatric systemic lupus erythematosus, psychiatric and neuropsychological syndromes, psychopathology, acute confusional state, delirium, cognitive disorder, anxiety disorder, mood disorder, depression, psychosis

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease of unknown etiology, mainly affecting women (9:1) especially of non-white descent (1, 2). A complex interaction among genetic, hormonal, immunologic and environmental factors is likely involved in its pathogenesis. Undoubtedly, immune dysregulation is a key event, and SLE is considered a paradigm for systemic autoimmunity (1).

The disease may affect any organ and system, including central, peripheral and autonomic nervous system (1-3). The reported prevalence of central nervous system (CNS) involvement in SLE varies from 19% to 91% in adult patients of different ethnicity (3-13), and from 17% to 95% in pediatric patients

(14-22), being the wide variability in frequencies likely related to different methods of patients' selection or assessment, and to different professional orientation of clinicians.

The SLE-related CNS disorders are clinically heterogeneous, focal or diffuse, transient or chronic; they may range from mild to severe, may often co-occur and potentially decrease patient span and quality of life, even representing the most devastating feature of the disease (3, 23-25). These manifestations are considered as primary when causally and directly attributable to the SLE physiopathology, which entails vasculitis, non-inflammatory vasculopathic changes, coagulopathy, pro-inflammatory cytokine effects, and autoantibody-mediated damage (interference with neurotransmission, loss of plasticity, and/or neuronal cell death) (24, 26-29). Immune-mediated injuries may depend on both autoantibody intrathecal production and their passage from the circulation across a permeabilized blood-brain-barrier (BBB) (28, 29).

Whereas focal organic SLE-related brain disorders (such as stroke and seizures) are primarily related to thrombotic or vasculitic events, the pathogenesis of diffuse brain syndromes is likely multifactorial (26, 27). Anti-phospholipid (aPL) and anti-ganglioside antibodies, as well as antibodies against ribosomal P proteins, *N*-methyl-D-aspartate receptor (NMDAR), glial fibrillary acidic protein (GFAP), microtubule-associated protein 2, neurofilaments, neuronal and endothelial cells, have been reported to play a relevant role (4, 10, 11, 27-31). Recently, the antibodies anti-triosephosphate isomerase, having as target a glycolytic enzyme strongly expressed in brain tissue and crucial in microtubule stabilization, have been proposed as marker of neuropsychiatric SLE (NPSLE) (32).

However, the CNS involvement in patients with SLE can also be indirectly related to the disease, and be secondary to infections, sepsis, hypertension, metabolic abnormalities, or iatrogenic factors (23, 24, 33, 34).

Moreover, the psychological impact of the disease and psychosocial stressors may condition the development of reactive psychopathology in SLE patients, which have to adjust to a chronic illness with a pattern of remissions and flares, generally occurring early in life and involving complex problems of self/body image, familial relationships, social functioning, working ability and, in women, of childbearing; coping challenges are particularly relevant in adolescence, when personality definition is ongoing and the role of body image and the fear of peer rejection are absolutely crucial (33, 35).

Regardless of etiology and attribution, the clinical significance of CNS disorders in SLE patients is strongly reflected by the adverse impact on patients' life and clinical outcome (8, 25).

According to the American College of Rheumatology (ACR) nomenclature, the term "NPSLE" identifies neurological and psychiatric syndromes that can either precede the disease onset or occur at any time during its course, and not attributable to other causes (36).

Following the ACR definition (36), NPSLE refers to three main clinical categories (Table 1): *1) neurological syndromes of the CNS*, including cerebrovascular disease, demyelinating syndrome, headache, aseptic meningitis, chorea, seizures, myelopathy; *2) neurological syndromes of the peripheral nervous system*, including acute inflammatory demyelinating polyradiculoneuropathy, mononeuropathy, autonomic disorder, plexopathy, polyneuropathy; *3) diffuse psychiatric/neuropsychological syndromes*, including cognitive disorder, acute confusional state (delirium), anxiety disorder, mood disorder, and psychosis, classified according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) terminology (37).

In the concerning literature, neurological and psychiatric manifestations of the disease are usually reported together, and specific data on SLE psychopathology are limited, notwithstanding the peculiar clinical presentation and physiopathology deserve separate assessment.

Thus, we aimed to electively focus on diffuse psychiatric/neuropsychological SLE syndromes (36), in both adult and pediatric patients, reviewing and discussing their prevalence, pathogenesis, diagnostic aspects, and current therapeutic options.

Methods

A detailed search was performed in the PubMed (U.S. National Library of Medicine) database, using

Table 1. The SLE neuropsychiatric clinical categories and corresponding disorders, according to the American College of Rheumatology nomenclature (36).

Clinical category	Corresponding disorders
Neurologic syndromes of central nervous system	Cerebrovascular disease Demyelinating syndrome Headache Aseptic meningitis Chorea Seizures Myelopathy
Neurologic syndromes of the peripheral nervous system	Inflammatory demyelinating polyradiculoneuropathy Mononeuropathy Autonomic disorder Plexopathy Polyneuropathy
Diffuse psychiatric/neuropsycological syndromes	Cognitive disorder Acute confusional state (delirium) Anxiety disorder Mood disorder Psychosis

the following key words: neuropsychiatric systemic lupus erythematosus, central nervous system, psychiatric syndromes, neuropsychological syndromes, psychopathology, cognitive disorder, acute confusional state, delirium, anxiety disorder, mood disorder, depression, psychosis.

Original publications and reviews were considered eligible when they dealt with distinct psychopathologies classified according to the ACR nomenclature system for NPSLE (36), defined following the DSM-IV terminology (37), and resulting from well-defined SLE cases (38, 39).

Results

Cognitive disorder

Cognition entails the intellectual functions that result in thought. Cognitive processes may be categorized in different domains (such as attention, memory, language, visual-spatial learning, psychomotor speed, executive function, and logic reasoning/problem solving), whose neurobiological substrates are provided by multiple integrated networks from cortical gray matter, subcortical gray matter, cerebral hemispheric white matter, and commissural tracts (40).

Cognitive disorder is one of the most frequent and studied SLE-related psychopathologic manifestations, reported with estimates ranging from 2.7% to 59.6% in adult patients (3, 5, 9, 10, 25, 30, 41-46) (Table 2), and from 4.7% to 59% in pediatric patients (14, 17, 18, 21, 22, 47). This wide range in frequency reflects methodological variability in subject selection, sample size, definition of cognitive impairment, formal testing methods, and variation in thresholds for positive tests (48,49). With this regard, reliable and valid instruments in order to measure cognitive deficit in SLE patients have been proposed, as well as criteria to define minimally important change for clinical trials (50, 51).

However, the real prevalence of cognitive disorder in SLE may be underestimated, owing to the neuropsychological assessment of patients is not routinely performed, requiring time and wholehearted co-operation, and being particularly challenging in pediatric patients. Computer-administered performance testing appears to be a promising screening method in both childhood and adulthood patients (47, 52).

Cognitive dysfunction may be present at any time during the SLE course, and in the apparent absence of

Table 2. The reported frequency of SLE-related cognitive disorder in adult patients

Authors (Reference)	Patients' number	Ethnicity	Cognitive disorder (%)
Hanly et al. (3)	111	Caucasian, Asian, African, Native American	2.7
Hanly et al. (25)	572	Caucasian, African-American, Asian	5.4
Hawro et al. (41)	52	Polish	9.6
Sanna et al. (10)	323	Caucasian	10.8
Mok et al. (5)	282	Chinese	12
Hanly et al. (42)	70	Canadian	30
Ainiala et al. (43)	46	Finnish	24
Mikdashi et al. (9)	130	African-American, Caucasian	27.3
Olazarán et al. (44)	31	Hispanic	32.3
Abdel-Nasser et al. (45)	32	Egyptian	37.5
Lapteva et al. (30)	60	Caucasian, African-American, Asian	46.6
Tomietto et al. (46)	54	Italian	59.6

disease activity or other NP manifestations (25, 49, 53-55). Patients with current or previous episodes of NPSLE appear to be at higher risk (33, 54). The clinical signs may be subtle and transitory, and most of patients display fluctuating and not cumulative patterns of deficit, while only a minority undergoes a severe and persistent cognitive decline (42, 46, 53), consistent with prevalently reversible underlying damage (26).

SLE cognitive impairment may involve all cognitive domains in varying degrees (25, 44), however, attention, verbal and working memory, logical reasoning and processing speed are the most frequently altered functions in adults (46, 49, 54-58), suggesting the main involvement of frontal and parietal areas (55); in childhood patients, complex problem solving, attention, visuomotor integration, verbal and working memory are prevalently affected (59).

The presence of chronic damage, measured by the Systemic Lupus International Collaborating Clinics/ACR Damage Index, arose as the main disease-related factor affecting the severity of cognitive disorder (46), which, however, was not always associated with excess morbidity (25, 42).

Hypertension appeared to be the most important generic cardiovascular risk factor influencing both the presence and severity of cognitive deficit in SLE patients (46, 60), and an independent effect of age was also observed (9, 46, 60), whereas high educational levels were found to display a protective effect, likely due to a greater functional brain reserve (46, 60).

The pathogenesis of SLE-related cognitive disorder remains not precisely elucidated, however, the role of ischemia (related to vasospasm, disease-associated accelerated atherosclerosis, small-vessel vasculopathy, or vasculitis) is generally accepted as prominent, with the possible contribution of coagulopathy and immune-mediated processes (26).

Notably, the Raynaud's phenomenon was found to positively correlate with the severity and the number of the impaired functions, underlining the relevant role of vessel spasm (46). The cerebral small-vessel vasculopathy (consisting of perivascular cuffing and remodelling of microvasculature, and attributed to the deposition of immune complexes in the vessel wall with participation of activated complement) can contribute (26, 46, 61). In SLE patients with cognitive impairment, small-vessel cerebral vasculopathy was found to be associated with significantly higher circulating concentrations of matrix metalloproteinase-9 (MMP-9), a zinc-containing endoproteinase able to degrade a variety of extracellular matrix components and implicated in various disease-related processes, including atherogenesis and BBB disruption. MMP-9 serum levels were found to positively correlate with the volumes of T1-weighted and T2-weighted lesions in the brain magnetic resonance imaging (MRI) (43). Moreover, in patients with SLE, associations between

cognitive dysfunction and microembolic signals have been also reported (62).

The potential role of aPL antibodies (especially if persistently present and at elevated titers) in the SLE cognitive disturbance development has been widely suggested (42, 46, 55, 60, 63). The prevalence of moderate/severe cognitive deficit was found to be significantly higher in aPL-positive patients with concomitant Raynaud's phenomenon, suggesting additive effects (46). Circulating antibodies against NMDAR have been demonstrated in SLE patients' brain, correlating with both neuronal damage and cognitive disorder (64).

Recently, the cerebrospinal fluid (CSF) levels of antibodies against the intermediate neurofilament alpha-internexin (INA), a protein expressed in differentiated neurons and involved in the cytoskeletal integrity maintenance, were found to be inversely related with the SLE patients' cognitive status; moreover, in a murine model obtained by INA immunization, pronounced cognitive impairment/memory loss and histopathologic evidence of profound cortical and hyppocampal neuron apoptosis were observed (65).

Cytokines and chemokines may play a contributing role in the SLE-related cognitive disorder occurrence (49), and a positive association between serum levels of interleukin-6 (IL-6) and both learning and attention deficit has been demonstrated (66).

Increased serum concentrations of vasopressin and calcitonin gene-related peptide, both involved in the control of human behavior and cognition, have been found in SLE patients with cognitive impairment (67).

Genetic polymorphisms have been suggested to influence the onset or progression of SLE cognitive deficit. Patients carrying the Met66 allele of brain-derived neurotrophic factor (BDNF) gene performed significantly better in attention and executive, psychomotor and motor domains, consistently with a genetic protective effect (68).

MRI has been proposed as the gold standard for the morphologic evaluation of NPSLE, including cognitive disorder, in both adult and pediatric patients (69, 70). White matter T2-weighted lesions, consisting of micro-ischemic insults, cerebral atrophy, and reduction in cerebral and corpus callosum volumes (46, 71-73), were found to be associated with cognitive disturbance in adult SLE patients; in pediatric patients, cerebral and cerebellar volume loss was observed in the majority of blinded prospective cohort MRI researches, while white matter hyperintensities were less frequently found (74).

However, MRI sensitivity and specificity in identifying abnormality patterns of SLE-related cognitive disorder is controversial (75-77), and the real correlations between the cerebral MRI findings and the severity of clinical manifestations are often inconsistent (46).

Single photon emission computed tomography (SPECT), a useful tool to evaluate brain perfusion, represents a highly sensitive method for NPSLE evaluation in both adulthood and childhood, but with a controversial specificity (78-80). In pediatric patients with no history of overt NPSLE, the presence of abnormal SPECT results suggested that, in children, subclinical CNS disease may be more common than expected (80). Recently, focal or diffuse reduction of γ-aminobutyric acid-A (GABA-A) receptor density measured by (123)I-labelled Iomazenil binding has been demonstrated on brain SPECT of SLE patients with cognitive defects. Such a GABA-A receptor density decrease might be related to the SLE cerebral vasculopathy, or to neuronal-reacting autoantibodies, or even to iatrogenic interferences with GABA-A receptor expression/binding (81).

Positron emission tomography (PET) with [^{18}F]2-fluoro-2-deoxy-D-glucose (evidencing impairment in brain glucose utilization) represents a sensitive method to detect manifest or subclinical CNS involvement in NPSLE patients without morphological changes, and PET findings have been demonstrated to well correlate with the disease clinical course (82, 83). SLE cognitive disorder was found to be associated with regional brain glucose hypometabolism, and fluctuations of the patients' cognitive profile corresponded to parallel changes on PET (84).

Evolving technologies, such as magnetization transfer imaging (MTI) and magnetization transfer ratio (MTR) (85-87), MR spectroscopy (MRS)/proton MRS (1H-MRS) (30), as well as diffusion-weighted imaging (DWI), T2 relaxometry, and functional MRI (FMRI) (61, 69, 88), may contribute in

improving the identification of subtle cerebral changes in NPSLE patients, including those with cognitive deficit.

Decreased peak height of MTR histogram of the whole brain was evidenced in NPSLE patients compared with controls, reflecting neuronal dysfunction (85-87), and lower MTR peak height was electively associated with cognitive impairment (87).

MRS imaging evidenced a correlation between cognitive disturbance and frontal white matter metabolic changes, in the absence of evident axonal damage or cerebral atrophy, supporting the role of microstructural white matter alterations (89).

1H-MRS is considered a promising, noninvasive imaging modality for the cognitive function assessment, providing the measure of biochemical metabolites, such as N-acetylaspartate (NAA), choline and creatine. The NAA concentration is recognized as index of neuronal density and integrity; change in choline levels is associated with membrane breakdown (possibly related to inflammation, demyelination or ischemia), and creatine value is thought to reflect intracellular energy stores (30). In SLE patients with cognitive disorder, several 1H-MRS studies showed reduction in the NAA:creatine or NAA:choline ratio and increase in the choline:creatine ratio (90-93); patients with moderate or severe deficit presented significantly higher choline:creatine ratio in the dorsolateral prefrontal cortex and white matter, compared with patients with mild or absent impairment (30).

In childhood patients, FMRI studies suggested that pediatric SLE may be associated with white matter connectivity dysfunctions, rather than injury of specific gray matter areas (88).

Undoubtedly, the neuroimaging patients' evaluation with conventional or evolving technologies may represent a useful corollary for the diagnosis of SLE-cognitive disorder, which, however, is essentially clinical and primarily requires a careful neuropsychological assessment.

The primary or secondary origin of cognitive deficit in SLE patients has to be identified, particularly with respect to the possible iatrogenic origin. In fact, cognitive impairment may represent a dose- and time-dependent adverse effect of synthetic glucocorticoids (SGCs), quite infrequent at prednisone-equivalent dose <20 mg/day (34). Whereas SGC low doses generally do not affect cognitive function in both short and long-term courses, high dosages may impair both hippocampus-mediated declarative memory and frontal lobe-mediated working memory in adult patients and may induce in pediatric patients severe disturbances in attention, concentration, memory retention, mental speed and efficiency. The SGC cognitive adverse effects are usually reversible in adult patients after SGC discontinuation, while children appear to be particularly susceptible (34). In differentiating the steroid-dependent cognitive dysfunction from the SLE primary disorder, the SGC dosage, the time interval, and the duration of mental changes may be helpful.

A universally accepted definition of the optimal treatment for SLE cognitive deficit is presently lacking. When the impairment is associated with signs of disease activity, the combination of addressed immunosuppressive treatment (to obtain the adequate SLE control) with cognitive rehabilitation (based on intensive retraining of cognitive skills) represents an efficacious approach in both pediatric (59) and adult SLE patients (94).

When coexistent with persistent aPL positivity, cognitive disorder may benefit from anticoagulation in selected patients; regular aspirin use was reported to be associated with improved cognitive function in older patients (60), while the role of antiaggregant therapy in childhood has to be defined. The use of vasodilators has to be taken into account in patients with Raynaud's phenomenon, and the effective control of arterial pressure in patients with hypertension is needful (46).

Acute confusional state

Acute confusional state (also categorized as delirium in the DSM-IV, and in the past termed "organic brain syndrome") is defined as disturbance of consciousness with reduced ability to focus, maintain, or shift attention, which can be associated with cognitive deficit and/or changes in mood, behavior, or affect (37).

Delirium poses serious threats, being the expression of severe, direct or indirect brain injuries, and de-

serves careful evaluation and aggressive treatment. It usually develops over a short time and tends to fluctuate, ranging from consciousness disturbances to coma, and entailing hyperaroused (extreme agitation, delirium tremens), hypoaroused (somnolence, stupor), and mixed states (37). Acute confusional state seems to depend on a dopaminergic/cholinergic imbalance: hyperactive delirium seems to originate with a high dopaminergic levels, leading to agitation and aggressiveness, whereas low or normal dopamine values predominate in hypoactive and mixed states, in both adult and pediatric patients (95).

In SLE patients, delirium has been reported with a frequency ranging from 1.7% to 19.6% in adults (3-5, 10, 25, 43, 96, 97), and from 0.9 to 35% in children (17, 22, 70).

The pathogenic mechanisms of such a severe SLE manifestation have to be clearly defined, however, vasculitis, hypoxemia, leukoencephalopathy due to small vessel vasculopathy, perivenous spongiform encephalopathy, brain edema, and immune-mediated neuronal dysfunction are thought to be involved (23, 26).

The diagnosis is electively clinical. In a prospective study evaluating the diagnostic reliability of CSF tests for acute confusional state [such as IL-6, IL-8, interferon (IFN)-α, and immunoglobulin (Ig)G index], the CSF levels of IL-6 and the IgG index showed significant associations with delirium in patients with SLE (98).

In adult SLE patient with acute confusional state, lower cortical thickness and subcortical gray matter reduction were observed on MRI in several regions of the brain (72). SPECT evidenced hypoperfusion in both frontal lobes, underlining the etiopathogenic role of ischemia; notably, after improvement of psychiatric symptoms, cerebral blood flow was found to parallel ameliorate (99).

At present, universally defined treatment strategies for the management of SLE-related delirium are lacking, and the available literature is mostly based on anedoctical reports (100, 101). In the first instance, the treatment generally requires intravenous (i.v.) pulses of SGCs in association with targeted psychiatric therapy, primarily based on first generation antipsychotics/neuroleptics (such as haloperidol and chlorpromazine), or second generation/atypical antipsychotics (such as risperidone, olanzapine and quetiapine) in both adult and pediatric patients (102, 103). In comparison with classical neuroleptics, atypical antipsychotic has a different receptor binding profile (lower binding to dopamine receptors, high affinity to serotonin receptors and β1 adrenoreceptors), low incidence of side effects (namely hyperprolactinemia and extrapyramidal symptoms, such as akatisia, dystonic reactions or dyskinesias), and appear to be safer than their precursor clozapine with regard to neutropenia or agranulocytosis (102).

Atypical antipsychotics vary in pharmacokinetic and in risk of specific adverse effects, but they have generally replaced older butyrophenone and phenotiazine neuroleptics. However, some peculiarity of the antipsychotic activity have to be considered: in patients with hyperactive delirium, risperidone (known to selectively increase dopamine levels in some pathways) may exacerbate certain elements of the hyperaroused state, particularly agitation, and is mainly addressed to treat patients with hypoactive/mixed delirium, while haloperidol is indicated for the treatment of extreme agitation states, in both pediatric and adult patients (95, 104).

Acute confusional states refractory to the SGC and antipsychotic combination may be controlled by the further administration of pulse i.v. cyclophosphamide therapy (105, 106).

Anxiety disorder

Anxiety is defined as unwarranted, inappropriate, and intense experience of fear and worry, whose neurochemistry is related in multiple brain regions to several neurotransmitters, such as glutamate, gamma amino butyric acid, and monoaminergic mediators (107).

The category "anxiety disorder" entails panic disorder and agoraphobia, specific (simple) phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, and mixed anxiety-depression (37).

Few studies have hitherto focused on such a psychiatric SLE (PSLE) manifestation. In adult patients, it has been reported with a prevalence ranging from

0.9 to 31.4% (3, 4, 10, 12, 25, 41, 108, 109), and from 0.9% to 21% in pediatric patients (17, 22). In Brazilian female patients with SLE, the anxiety disorder lifetime prevalence was estimated as 52.1% (110).

The pathogenic mechanisms leading to the development of such a SLE manifestation are presently undefined: a role for genetic predisposition, coping difficulties, or presently unknown factors of biological origin has been suggested (26).

The diagnosis is electively clinical and, presently, no specific neuroimaging features have been reported in SLE patients with anxiety disorder.

Selective serotonin-reuptake inhibitors (SSRIs), such as fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram, serotonin-noradrenalin reuptake inhibitors (SNRIs), including duloxetine, venlafaxine, or buspirone, are well-established treatments for anxiety disorder in adult patients (111), and SSRIs have been found to provide positive effects also in pediatric patients (112). Although there are no defined SSRI dosing guidelines for children and adolescents, dose studies suggest starting low, monitoring closely for side effects, titrating to a minimally effective dose, and, eventually, increasing after 4-6 weeks if significant improvement is not achieved. SSRIs should be maintained at the minimal effective dose for at least 6-12 months, and, then, slowly tapered until stop (112).

The patients receiving SSRIs should be carefully monitored for irritability, sleep problems, increased motor activity, and akathisia, as well as for suicidal thoughts and behavior (108).

In acute phase, when a rapid reduction in severe anxiety symptoms is required, benzodiazepines may provide useful and effective anxiolytic activity, representing a short-term adjunctive treatment with SSRIs. In fact, when prescribed for >4 weeks, benzodiazepines may cause withdrawal symptoms and rebound anxiety (111).

Evidence supports the complementary efficacy of cognitive-behavioral therapy in both adult and pediatric patients (111, 112); in childhood anxiety, the combination of SSRI treatment and cognitive-behavioral therapy has been found to provide superior response rate (113).

Mood disorder

Mood disorder identifies an overarching category, often synonymously defined as "affective disorder". Actually, the former term refers to the underlying or longitudinal emotional state, while the latter refers to the external expression observed by others.

Mood disorder includes cyclothymic disorder, schizoaffective disorder, minor and major depression, recurrent brief depression, bipolar disorder type I (BP-I) and II (BP-II) or cyclothymia, catatonia and melancholia (37). However, two main groups are broadly recognized, such as depressive disorders, whose prototype is major depressive disorder (MDD) (commonly called major depression or clinical depression), and bipolar disorders, entailing BP-I and BP-II.

MDD disorder is a clinical syndrome lasting at least 2 weeks, during which the patient experiences either depressed mood or anhedonia, plus at least 5 of the following symptoms: depressed mood most of the day, nearly every day; markedly diminished interest or pleasure in most activities most of the day; significant weight loss or gain or appetite disturbance; insomnia or hypersomnia; psychomotor agitation or retardation; inappropriate guilt; diminished ability to think or concentrate or indecisiveness; or recurring thoughts of death, including suicidal ideation (37).

BP-I is characterized by episodes of mania which corresponds to elevated (euphoric) and/or irritable mood, plus at least three of the following symptoms (four, if mood is only irritable): grandiosity, decreased need for sleep, increased talking, racing thoughts, distractibility, overactivity (an increase in goal-directed activity), psychomotor agitation and excessive involvement in risky activities. BP-I completely impairs the interaction with the external world, until disconnection from reality, while BP-II is described by episodes of hypomania (namely, lowered states of mania), not severe enough to cause marked impairment of social or occupational functioning (37). Therefore, the symptoms of mania (defining BP-I) and hypomania (defining BP-II) are the same, but mania is more severe and may require hospitalization.

In adult SLE patients, the mood disorder frequency has been reported with estimates ranging from 2.7% to 59.4% (3, 4, 10, 12, 25, 41, 45, 108, 109), and

from 3% to 57% in pediatric patients (14, 17, 22, 70). The lifetime prevalence of mood disorder was estimated as 69%, in Brazilian female SLE patients (110), and as 47%, in a large cohort of Caucasian female patients, resulting two times more common than in general population (114).

Clinicians should be aware that SLE patients with mood disorder deserve careful attention for suicidal behavior risk (108, 115). In a study analyzing the records of 300 SLE patients over 20 years follow up, 2% of subjects made suicide attempts, fatal in one case. The median age of attempting patients was 41 years and median disease duration was 2.5 years. The median time from the onset of SLE-related psychopathology to the suicidal attempts was 12.5 months (115).

The pathogenetic mechanisms of SLE-related mood disorder are not clearly identified, however, immunologically-mediated neuronal dysfunction (due to diffusely distributed antibody- or immune complex-dependent brain injury, or focally distributed, with cortical micro-infarct or thromboembolism) may be involved, with the possible contribution of hereditary vulnerability and coping difficulty (26).

Anti-ribosomal P antibodies have been suggested to be the PSLE specific markers, and particularly of depression and psychosis (25, 29, 116, 117). These antibodies cross react with a protein of high molecular mass exposing P epitope (p331) on neuronal surface of specific brain areas, such as amygdala (involved in arousal and emotional responses), ventral tegmental area (involved in reward processing and drug addiction) and cortex and hippocampus (involved in memory and higher brain functions), mediating calcium influx and neuronal cell apoptosis (29). Notably, in a murine model obtained by intracerebroventricular injection of affinity-purified human anti-ribosomal P antibodies or IgG as control, the administration of human anti-ribosomal P antibodies was found to induce depression-like behavior (118).

However, the "psychopatogenic" potential of anti-ribosomal P antibodies is not widely accepted, being the prevalence of these autoantibodies highly variable in patients, time fluctuating, and depending on different ethnic backgrounds, sensitivity and specificity of the assays employed for the detection (119). Furthermore, an international meta-analysis affirmed that the value of anti-ribosomal P antibody testing for the diagnosis of NPSLE overall or for particular phenotypes should be considered as negligible (7).

In SLE patients with depressive symptoms, higher serum values of antibodies against NMDAR subunit NR2 have been found (30); moreover, a relationship between antibodies against endothelial cells (AECA) and mood disorder has been suggested (109).

At present, no specific MRI features or peculiar alterations in neurometabolite concentrations on MRS have been demonstrated (30). Ischemic white-matter hyperintensities were found with similar frequency in depressed and nondepressed patients with SLE (120). SLE patients with mood disorder and without MRI lesions showed abnormal CBF on 99mTc-ethylcysteinate dimer (99mTcEDC) SPECT assessment, with flow reduction in the cingulated gyrus and thalamus (121). A significant CBF decrease was observed in bilateral frontal and temporal cortex of female SLE patients with depression, being the greater reduction in the more superior part of the frontal lobe extending to premotor and motor areas. This pattern is not typical of MDD, in which the prefrontal cortex is predominantly affected, and, therefore, the topography of CBF defects in SLE-related depression and MDD does not overlap (120).

The main differential diagnostic problems usually concern whether mood disorder is "due to a general medical condition" or "comorbid" (37), or whether it might represent a SGC-related adverse effect (which is generally associated with long-term treatments, is usually reversible with treatment discontinuation or reduction, and often restarts on dose increase/re-administration) (34). A careful clinical history and temporal relationship evaluation, an accurate mental status and psychological profile examination may be the orienting tools.

SLE-related mood disorder requires immunosuppressive therapy to achieve the adequate disease activity control, in association with antidepressant treatment and psychotherapy. Second-generation antidepressants, such as SSRIs and SNRIs, have similar efficacy to and lower toxicity than first-generation antidepressants (tricyclics and monoamine oxidase inhibitors). The choice of a specific drug depends on

both the clinical picture and the potential side effects. For example, tricyclics may be useful in patients suffering from chronic pain, but their anticholinergic side effects may be unacceptable.

Patient status, therapeutic response, and adverse effects of antidepressant therapy have to be carefully assessed on a regular basis, beginning within 1 to 2 weeks of initiation, and, if the patient fails to present benefits within 6 to 8 weeks, the treatment has to be modified. In severe cases, the combination of an antidepressant with an antipsychotic of second generation is requested, in association with high-dose SGC therapy. In refractory patients, pulse i.v. cyclophosphamide regimen can be proposed (106). Electroconvulsive treatment may be required in selected cases (122).

Lithium therapy is effective in the treatment of bipolar disorders; in patients with intolerance or contraindications for lithium therapy, valproate and carbamazepine can obtain positive results. Other anticonvulsants (lamotrigine, gabapentin and topiramate) are currently being tested. Atypical antipsychotics appear to be of interest in the BP-I treatment, both as monotherapy and as add-on maintenance therapy with lithium or valproate (123).

Benzodiazepines play a very limited role in the treatment of depression: they are recommended for short-term treatment, if the patient presents depression with symptoms of anxiety, agitation, or insomnia, or acutely suicidal depression (124). Moreover, benzodiazepines may be efficacious for catatonia, a rare aspect of SLE mood disorder, defined by catalepsy, stupor, negativism, mutism, posturing, stereotypies, mannerism, grimacing, echolalia and echopraxia, and likely related to neurobiological GABA- and NMDA-mediated mechanisms (122). Not all cases of catatonia respond to benzodiazepines, requiring high-dose SGCs and/or cyclophosphamide or plasmapheresis, in association with second generation antipsychotics, and, in unresponsive cases, with electroconvulsive therapy (122).

Psychosis

Psychosis is defined as a severe alteration in the perception of reality, characterized by thought disturbance, hallucinations, illusion and/or delusion, causing clinical distress or impairment in social, occupational, or other relevant areas of functioning. Withdrawn, aggression, suicidality or homicidal tendencies may characterize it.

Few studies have specifically focus on such a SLE-related psychiatric syndrome. Psychosis has been described in 1.9 to 30.3% of adult SLE patients (Table 3) (3-5, 9, 10, 12, 25, 41, 96, 109, 125-127), and in 2.8 to 36% of pediatric patients (14, 17-19, 22, 70).

Psychosis has been mainly reported as a SLE initial presentation or as early finding (96, 125, 126). It usually occurs in the context of florid clini-

Table 3. The reported frequency of SLE psychosis in adult patients

Authors (Reference)	Patients' number	Ethnicity	Psychosis (%)
Hawro et al. (41)	52	Polish	1.9
Pego-Reigosa et al. (125)	485	Caucasian, Afro-Caribbean, Asian	2.3
Hanly et al. (3)	111	Caucasian, Asian, African, Native American	2.7
Hanly et al. (25)	572	Caucasian, Asian, African-American	2.9
Conti et al. (109)	51	Italian	3.9
Brey et al. (12)	128	Caucasian, African American	6.5
Sanna et al. (10)	323	Caucasian	7.7
Mok et al. (4)	518	Chinese	11
Appenzeller et al. (126)	520	Brazilian	11.3
Mok et al. (5)	282	Chinese	12
Kasitanon et al. (96)	91	Thai	13.3
Mikdashi et al. (9)	130	African-American, Caucasian	15.1
Adelowo et al. (127)	64	African	30.3

cal/serological activity of the disease (125, 126), and often patients show additional psychiatric/neuropsychological syndromes, such as depression, anxiety, or cognitive disorder (125).

SLE patients with psychosis must be considered at greater risk for suicidal attempts. Despite the relevance of this phenomenon, the concerning literature is presently scarce. In a study on clinical records of suicidal SLE patients, the majority of attempting subjects were psychotic (128). All the patients attempted suicide shortly after admission (mean time 20 days). The subsequent courses of the survivors who received more aggressive medication were favourable (128).

The pathogenesis of this diffuse PSLE syndrome is likely multifactorial. Clinical-serologic associations have been reported between SLE psychosis and anti-ribosomal P antibodies (117), AECA (109), aPL positivity (126), and anti-deoxyribonucleic acid (DNA) autoantibodies (9), but these findings require further confirmations.

Enhanced values of IFN-α were demonstrated in the CSF of patients with SLE psychosis, but not of patients with seizures, and IFN-α levels were found to decrease when psychotic manifestations subsided (129).

Iconographically, SLE psychosis has not been associated with specific morphologic changes, and brain MRI analyses can evidence either normal findings, or mild cortical atrophy and increased intensity signals in frontal white matter (125).

In differential diagnosis, the main problem usually consists in discriminating the primary from the secondary origin of psychotic episodes (e.g., due to sepsis, dysionia in advanced lupus nephropathy or to SGC treatment). Clinical picture, temporal relationships, SGC dose in use, and laboratory investigations may be helpful. In this regard, SGC-induced psychosis usually affects patients treated with more than 40 mg/day of prednisone or equivalent, mostly manifests within the first weeks (sometimes within few days) of the administration, and generally displays rapid resolution after SGC reduction or discontinuation. BBB damage and hypoalbuminemia have been proposed as related risk factors (34).

Standardized treatment strategies for SLE psychosis are not presently defined. The combination of SGC high-doses with classical or atypical antipsychotics usually obtains positive effects. In refractory cases, antidepressants, anxiolytics, pulse i.v. cyclophosphamide therapy, and plasmapheresis may be required (125, 130). Favourable results have been reported with oral cyclophosphamide followed by azathioprine maintenance (131). In children, treatment consisting of atypical antipsychotics, SGC high doses, and a second line agent (such as cyclophosphamide or azathioprine) is commonly proposed (18, 132, 133).

Intravenous immunoglobulins, mycophenolate mofetil, rituximab, intratecal methotrexate and dexametasone deserve further studies to confirm their usefulness in treating SLE psychosis (106, 134).

If early recognized and promptly treated, SLE-related psychosis has a usually complete recovery, and long-term outcome appears to be favourable in both adults (125) and children (15,18,133). However, relapses are not uncommon, consistently with autoantibody- and/or cytokine-induced reversible neuronal dysfunctions (23).

Discussion

Diffuse psychopathological syndromes are frequent and relevant manifestations of SLE, whose prevalence might be even underestimated, since formal neuropsychological/psychiatric evaluation is not routinely performed in all patients. In this regard, a systematic neuropsychiatric assessment to provide prompt diagnosis should be critical part of the SLE patients' clinical protocol, and universally accepted and validated evaluating tools should be performed and introduced in the clinical practice.

Moreover, due to the high suicidality risk reported in PSLE patients, recently estimated as 9.6% (108), careful assessment and greater clinician awareness may help to reduce the incidence of this potentially fatal event.

The PSLE pathogenesis is likely multifactorial: ischemia (due to disease-related vascular injury or cerebral vasospasm) and inflammatory/immunopathologic mechanisms appear to be the main factors affecting the development and severity in patients. Brain-specific and systemic autoantibodies have been

causally related to diffuse PSLE syndromes: aPL (especially if persistently present and a high titres) and anti-NMDAR antibodies have been reported to be involved in cognitive disorder development, while anti-ribosomal P antibodies have been suggested to play a role in the psychosis and mood disorder occurrence in adult SLE patients, but these associations require confirmation.

In childhood patients, no clear correlations between PSLE and autoandibodies have been presently reported, however, a predictive role of serum anti-ganglioside M1 antibodies has been recently suggested as reliable parameter for early diagnosis and management of NPSLE, before clinical manifestations, and a significantly positive association between anti-ganglioside seropositivity and cognitive disorder has been reported (135).

Associations between psychosis and enhanced CSF levels of IFN-α have been observed, as well as between serum levels of IL-6 and cognitive deficit. C-C chemokine ligand 5/RANTES, C-X-C chemokine ligand 9/MIG, IL-8, and IL-6 have been found to be significantly increased in CSF of patients with acute confusional state and psychosis, potentially mediating events that promote neuronal damage or dysfunction (136).

Significantly high CSF levels of neuronal and astroglial cell degradation products, such as the light subunity the neurofilament triplet protein (NFL) and GFAP, have been found in SLE patients with psychiatric/neuropsychological syndromes, suggesting neuronal destruction and astrogliosis. Of note, intrathecal levels of both NFL and GFAP showed a significant correlation with MRI abnormalities, and the successful cyclophosphamide treatment resulted in significantly decreased CSF levels of these proteins (137).

Animal models provided interesting pathophysiologic suggestions for human PSLE. In MRL/lpr lupus-prone mice, marked emotional reactivity and behavior changes, as well as deficits in spatial learning/memory tasks, appear as early as 7 weeks of age, and coincide with the emergence of humoral autoimmunity, antedating other autoimmune disease manifestations. In mouse brain, gliosis and neuronal loss are evident in the gray matter, the dendritic complexity of pyramidal neurons is strikingly reduced, and the hippocampus displays reduced neuronal density (138). The depression-like behavior of MRL/lpr mice was found to be significantly related with gender, and with titres of autoantibodies against nuclear antigens, anti-NMDAR, and anti-ribosomal P protein: young MRL/lpr females exhibited significant depressive behavior as early as 5 weeks, at which time elevated levels of autoantibodies were already present, as compared to MRL/lpr males, suggesting the primary role of autoantibodies in the pathogenesis of early neuropsychiatric deficits in this lupus model, which translate into gender-based differences in clinical phenotype (139). Notably, in lupus-prone mice, the early immunosuppressive treatment with cyclophosphamide attenuates aberrant behavior and memory deficits, and prevents neuronal atrophy of dendritic spines (140).

Ultimately, systemic/local immune/inflammatory networks, microvasculopathy, endothelial injury, and BBB breakdown (with the consequent brain access of lymphocytes, serum molecules, autoantibodies, leukocyte and platelet thrombi) may overall induce direct/indirect harmful neuronal cytopathic effects and hypoperfusion, leading to cell inactivation and damage in patients. The persistence of these processes may result in axonal/neuronal loss and atrophy, possibly associated to demyelination and gliosis. SLE neuropsychological/psychiatric syndromes may result from these insults, being the clinical picture determined by the nature of the injury and the prevalent neural networks implicated.

SLE psychopathologies must be promptly and correctly identified: when they are the presenting feature of the disease, the patient's global assessment (clinical and psychiatric/neuropsychological examination, serological and CSF investigations, conventional and advanced neuroimaging analyses) may support the diagnosis. In a patient with established SLE, the appearance of psychiatric/neuropsychological symptoms requires a careful consideration of all possible etiologies, evaluating if they are directly disease-related or not, and eventually identifying their secondary origin. In this respect, historical chronology, detailed global clinical, neuropsychic, and serological patients' assessment, as well as the disease activity determination, are needed.

The diagnostic complexity of the heterogeneous PSLE syndromes has spurred the search for diagnostically specific laboratory or imaging features that, however, have not been definitely identified.

In studying PSLE patients, MRI has been considered one of the most available and accessible imaging modality for the non-invasive evaluation, peculiarly useful in detecting and anatomically locating brain lesions, but its sensitivity and specificity appear to be limited. In fact, not all patients with obvious psychiatric/neuropsychological syndromes display verifiable MRI lesion, while patients without symptoms may present MRI abnormalities. Moreover, the MRI scanning does not allow to distinguish between acute and chronic brain injury (141).

Other brain imaging technologies, such as SPECT and PET, appear to be sensitive modalities, but have poor specificity for differentiating reversible *versus* irreversible injuries, old *versus* new alterations, and SLE-related from unrelated abnormalities.

Since neurometabolic impairment, neurochemistry or perfusion abnormalities may precede anatomic lesion, new functional techniques, such as MRS, DWI, and MTI, may allow to detect subtle pathologic brain changes not revealed by conventional instruments.

An integrated diagnostic approach coupling clinical evaluation with morphological and functional imaging modality may provide the best results.

No prospective randomized studies on PSLE treatment are presently available. Pharmacologic (immunosuppressive and psychiatric) therapy is basically targeted to suppress the disease-related mechanisms of tissue injury, to alleviate psychopathologic symptoms, and to prevent future pathology.

Recently, using an evidence-based approach followed by expert consensus, recommendations for the management of SLE with NP manifestations have been proposed (142). Treatment is primarily dictated by the severity of symptoms: for mild PSLE manifestations appearing without evidence of systemic disease activation, basic immunosuppressive therapy associated with symptomatic psychiatric treatment and cognitive-behavioural support may obtain positive effects; moderate/severe PSLE syndromes generally require high doses of SGCs, alone or in combination with azatioprine or cyclophosphamide (142), as well as targeted psychiatric therapy, psychosocial support, and family counseling. In severe manifestations refractory to standard immunosuppressive therapy, plasma exchange, intravenous immunoglobulins, and rituximab (anti-CD20 monoclonal antibody) may provide beneficial results, as well as intratecal methotrexate and dexametasone (142).

With respect to the targeted psychological/psychiatric approach, patients with mild anxiety symptoms and limited functional impairment may improve with cognitive-behavioral therapy, whereas patients with moderate/severe anxiety disorder require the combination of psychotherapy and SSRIs. Second generation antidepressant SSRIs and SNRIs are efficacious to treat major depression, while lithium therapy, valproate or carbamazepine are electively indicated for the treatment of bipolar disorders.

Old and newer antipsychotics are needed to treat SLE-related psychosis and delirium, as well as severe mood disorder, in selected cases and in association with SSRIs/SNRIs. Of note, while the underlying mechanisms remain to be completely elucidated, the evidence for a neuroprotective effect of atypical antipsychotics has been reported, since they may counteract some progressive deteriorative events by enhancing synaptic plasticity and cellular resilience. In different animal models of neurotoxicity, atypical antipsychotics were found to attenuate both cognitive and non-cognitive behavioral impairments, increase neurogenesis, upregulating the levels of BDNF, and reduce neuronal apoptosis, increasing the expression of Bcl-2 and modulating the Bcl-XL/Bax ratio (143).

Recently, tolerogenic peptide, a synthesized peptide based on the sequence of the complementarity-determining region 1 (hCDR1) of a human monoclonal anti-DNA antibody (Edratide), was found to ameliorate the clinical manifestations in murine lupus models, via down-regulation of pro-inflammatory cytokines and apoptosis, up-regulation of the immunosuppressive cytokine transforming growth factor-β, and induction of regulatory T-cells (144). Notably, in a study evaluating the SLE-related CNS pathology in lupus-prone (NZBxNZW)F1 (NZB/NZW) mice and the effects of hCDR1 treatment, diseased animals with increased anxiety-like behavior and memory

deficit showed significant improvements, suggesting that hCDR1 might be a novel candidate for the specific treatment of PSLE (145). Further studies are needed to evaluate the role of this possible therapeutic option.

In studying the protean group of SLE-related psychopathologies, evidence emerges that the exceptional complexity of the nervous system dictates the need of multidisciplinary researches, bringing together the disciplines of rheumatology, immunology, radiology, neurology, and psychiatry. A multidisciplinary approach not only will contribute to elucidate the pathophysiological substrate, but may also offer the greatest hope for developing targeted therapies.

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Correspondence: Delsante Giovanni
Dipartimento Polispecialistico
Medicina Interna e Reumatologia
Azienda Ospedaliero-Universitaria di Parma
Via Gramsci, 14
43126 Parma (Italy)
E-mail: gdelsante@ao.pr.it