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Clinical profile of patients with lupus psychosis in a Colombian cohort

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SUMMARY

The objective of this study is to describe the frequency and the clinical, paraclinical, and treatment profile of patients with lupus psychosis in a Colombian cohort of patients with systemic lupus erythematosus (SLE).

This retrospective cohort study evaluated epidemiological and clinical characteristics, results of neuroimaging, analysis of the cerebrospinal fluid, treatment, and disease evolution in patients with lupus psychosis.

Among 2,479 patients with SLE, six female patients aged between 20 and 50 years with a diagnosis of lupus psychosis were identified. In two patients, psychosis was present at disease onset and in the other four, SLE was already present, although the majority of them were diagnosed less than two years prior to the onset of psychosis. The entire cohort had high disease activity as measured by SLEDAI-2K. We found concomitant cutaneous, joint, and hematological alterations. Cerebrospinal fluid data were obtained in half of the patients and were normal. We performed brain tomography on most of our patients, which was almost always described as normal. In 5 out of 6 patients, the induction therapy to treat psychosis was based on steroids, and in the majority of them, a resolution of psychiatric symptoms was observed after initiating treatment.

Lupus psychosis is a rare event that usually occurs early in the course of the disease and is associated with other manifestations of SLE. This investigation mainly found concomitant cutaneous, joint, and hematological manifestations, with a favorable outcome after treatment, as described in the literature.

Key words: *Neuropsychiatric lupus, systemic lupus erythematosus, psychosis.*

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INTRODUCTION

Among the nineteen neuropsychiatric syndromes described in systemic lupus erythematosus (SLE), mood disturbances, anxiety, and psychosis are those with distinct psychiatric features (1, 2). The relationship between psychosis and SLE has been recognized for decades. However, it was only until 1999 that the American College of Rheumatology (ACR) defined a uniform definition of psychosis as part of neuropsychiatric lupus (3). Later, in 2010, the European League Against Rheumatism (EULAR) published recommendations for diagnosing, preventing, and treating neuropsychiatric systemic lupus erythematosus (NPSLE) manifestations. They also reported the cumulative incidence among the nineteen NPSLE syndromes; those considered rare <1%) were psychosis, myelitis, chorea, cranial neuropathies, and aseptic meningitis psychosis (4).

Although lupus psychosis is unusual and the coexistence of multiple factors such as concomitant drugs and infections may make it difficult to identify its causal relationship with SLE, it is one of the most dramatic clinical presentations. Delusions and hallucinations (visual and auditory) are the most striking features of the onset of lupus psychosis. Its low incidence has limited the number of clinical trials and the consensus on its treatment (1). We describe the clinical and laboratory profile of patients with lupus psychosis in a cohort of SLE patients from a university hospital.

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MATERIALS AND METHODS

In a cohort of 2,479 patients with SLE identified according to ACR/EULAR 2019 or SLICC 2012 classification criteria seen between the 1st of January 2012 and the 31st of December 2020 at Hospital San Vicente Fundación (Medellín, Colombia), those meeting the ACR 1999 case definition of lupus psychosis for NPSLE manifestations were evaluated. In addition, all cases were assessed with the previously described models of at-

Table I - Clinical and paraclinical characteristics of patients with lupus psychosis.

Sex/Age/ associated SARDs	Non-neuropsychiatric manifestations of SLE	Manifestations of neuropsychiatric lupus	Laboratory	Imaging studies	SLEDAI-2K	Time between SLE diagnosis and lupus psychosis (years)
Female / 48	Weight loss, discoid lupus, polyarthritis, leukopenia, and pericarditis	Visual and auditory hallucinations, delusions of grandiosity and mysticism, cognitive dysfunction	Hb 8.6 mg/dL, ESR 100 mm/h, CRP 1.2 mg/L, low C3, low C4, ANAs 1:2560 homogeneous, anti-dsDNA 1:640, normal CSF	Simple brain tomography: normal	19	2
Female / 49/ APS	Polyarthritis, autoimmune hemolytic anemia, lymphopenia, and bilateral pleural effusion	Auditory command hallucinations, paranoid ideation, mania, aggressiveness, cognitive dysfunction, and depression	Hb 11.6 mg/dl, ESR 20 mm/h, CRP 3.5 mg/L, low C3, low C4, ANAs 1:640 homogeneous, negative anti-dsDNA, normal CSF	Simple brain tomography: normal	17	1
Female / 16	Malar rash, oral ulcers, and polyarthritis	Auditory and visual hallucinations, paranoid ideation, catatonia, and depression	Hb 9 mg/dl, ESR 58 mm/h, CRP 0.7 mg/L, low C3, low C4, ANAs 1:2560 homogeneous, anti-dsDNA 1:160, normal CSF	Simple brain tomography: normal. Contrast-enhanced lumbosacral MRI: normal	20	2
Female / 21	Weight loss, fatigue, polyarthritis, anemia, lymphopenia, severe thrombocytopenia, microhematuria, sub-nephrotic proteinuria, vasculitic purpura in lower limbs, and peripheral neuropathy	Maniform psychosis, visual hallucinations, depression, agitation, and cognitive dysfunction	Hb 9 mg/dl, ESR 112 mm/h, CRP 48 mg/L, low C3, low C4, ANAs 1:1280 homogeneous, anti-dsDNA 1:1280, no CSF data	Simple brain MRI: small thalamic infarcts. EMG: motor and sensory axonal polyneuropathy	34	0
Female / 38	Raynaud's phenomenon, and polyarthritis	Paranoid ideation, and suicidal attempt	Hb 12.7 mg/dl, ESR 24 mm/h, CRP 1.0 mg/L, low C3, low C4, ANAs 1:40 homogeneous, negative anti-dsDNA, no CSF data	Simple brain tomography: frontal and left occipital encephalomalacia (because of the previous stroke)	14	14
Female / 29	Alopecia, discoid lupus, and myalgias	Delusion of grandiosity, incoherent language, and maniform behaviors	Hb 8.4 mg/dl, ESR 92 mm/h, CRP 17.6 mg/L, low C3, low C4, ANAs 1:160 homogeneous, anti-dsDNA1:10, no CSF data.	Simple brain tomography: normal	16	0

SARDs, systemic autoimmune or rheumatologic diseases; SLE, systemic lupus erythematosus; Hb, hemoglobin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANAs, antinuclear antibodies; anti-dsDNA, anti-double-stranded DNA antibodies; CSF, cerebrospinal fluid; APS, antiphospholipid antibody syndrome; MRI, magnetic resonance imaging; EMG, electromyography.

tribution of neuropsychiatric events in SLE (3-6). The patients with psychosis due to electrolyte, metabolic, toxic, and pharmacological causes were excluded. Demographic, clinical, laboratory, imaging, treatment, and outcome variables were evaluated.

The disease activity was assessed using the previously validated SLEDAI-2K score. This score includes 24 items and each descriptor has a different weight between 1 and 8. These manifestations were present at the time of evaluation or in the preceding ten days (7).

RESULTS

Of the 2,479 patients in the cohort, six (0.24%) had psychosis. All were women with a mean age of 33.5 years (range 16 to 49 years), and one patient also had an associated antiphospholipid syndrome. In two patients, psychosis was present at the onset of SLE. The psychotic manifestations were visual and auditory hallucinations in four patients and hallucinations with paranoid ideation in three patients. Two patients had both manifestations. Polyarthritis was the most common concurrent clinical finding and was present in 5 patients. All patients had C3 and C4 hypocomplementemia, five had positive anti-double-stranded DNA, and five had anemia. All had high disease activity with a mean SLEDAI-2K of 20±6.5. Three patients had lumbar punctures, all with normal cerebrospinal fluid (CSF), and neuroimaging was normal in four of the six patients. Table I describes the patients' clinical, laboratory, and imaging characteristics.

Regarding treatment, four patients received methylprednisolone pulses, another one received high-dose oral prednisolone, and three patients were treated with IV cyclophosphamide. In one case, IV immunoglobulin was used after the glucocorticoid pulses, due to infectious complications. Four patients were managed concomitantly with antipsychotics such as haloperidol, olanzapine, or quetiapine. Psychiatric symptoms resolved entirely in five patients, and one patient died of infectious complications. Table II describes the treatment of all patients in detail.

DISCUSSION

Our study found a low proportion of patients with SLE and lupus psychosis. This psychiatric alteration was an early manifestation of SLE in most cases, similar to the findings reported in other investigations, in which the prevalence of lupus psychosis varies between 0 and 11% (2, 8). Hanly et al. published a prospective multi-ethnic cohort of patients with SLE; among 1826 patients, there were 31 psychotic events (1.53%). In most patients, this event was attributed to SLE and usually occurred within the first year after diagnosis of the disease (1). In an-

Table II - Treatment data in six patients with lupus psychosis.

Previous steroids use (dose and time)	Lupus psychosis and additional manifestations of SLE management	Use of psychotropic drugs	Outcomes
PDN 15 mg/d; 16 months	PDN 60 mg/d	Haloperidol, then quetiapine plus trazodone	Complete resolution of psychiatric symptoms
PDN 50 mg/d; 9 months	CYC	Valproic acid	Complete resolution of psychiatric symptoms
PDN 15 mg/d; 4 months	MTP for 5 days, total dose 2.5 g + CYC	Haloperidol then olanzapine plus lorazepam	Complete resolution of psychiatric symptoms
Without previous steroids use	MTP for 3 days, total dose 1.5 g + CYC	Olanzapine plus levomepromazine	Complete resolution of psychiatric symptoms
PDN 5 mg/d; Unknown time	MTP for 3 days, total dose 1.5 g	Fluoxetine	Complete resolution of psychiatric symptoms
PDN 20 mg/d; 5 months	MTP for 3 days, total dose 1.5 g + IV Ig	Quetiapine	Infectious complications that led to death

LES, lupus eritematoso sistemico; PDN, prednisolone; CYC, ciclofosfamide; MTP, metilprednisolone; IV Ig, immunoglobulina endovenosa.

other cohort, it was reported that 80% of lupus psychotic episodes occurred within the first year of SLE diagnosis (2).

Due to the broad differential diagnosis in lupus patients, psychosis should be interpreted cautiously in the emergency setting; symptomatic treatment is essential while investigating etiologies such as infections, metabolic and electrolyte disturbances, or psychoactive substance abuse, among others (9).

Similarly, psychosis in patients with SLE could be a consequence of glucocorticoid treatment. Only one patient had no previous exposure to glucocorticoids in our study, and it is not always easy to differentiate drug-related side effects from lupus manifestations. It is essential to note that it is unusual for glucocorticoid psychosis to present with doses ≤40 mg/day of prednisolone or equivalents. Frequently, those receiving short-term treatment with steroids present with euphoria or hypomania, whereas long-term treatment tends to generate depressive symptoms. Furthermore, most psychiatric symptoms secondary to glucocorticoids occur in the first 1 to 2 weeks of use (10, 11). These data could help the clinician to differentiate lupus psychosis from steroid-induced psychosis. The possibility of using biomarkers to differentiate lupus psychosis from steroid-induced psychosis, such as IL-6 in CSF, serum albumin or anti-ribosomal P, anti-neuronal, anti-phospholipid antibodies, among others, has even been raised (8, 12-14). Most of the markers reported in the literature were not measured in our patients. However, the included cases were thoroughly evaluated based on previously designed attribution models before the diagnosis of lupus psychosis was considered (15).

In this series, we mainly found concomitant cutaneous, joint, and hematologic involvement, as previously reported in the literature (2). Vasculitic manifestations and pleuritis were not as frequent as in other studies (2, 16). Similar to what we found in this study, others have described that patients with lupus psychosis had high disease activity (6).

The usefulness of CSF testing lies mainly in excluding other etiologies. The CFS is generally normal in lupus psychosis, although findings suggestive of generally mild neuroinflammation may be found in a minority of cases (2, 8, 9). Similar to the findings reported by other authors, we obtained CSF data in half of the patients in our cohort, all of which were normal. Brain tomography was performed in most of our patients and was almost always described as normal. The brain imaging technique of choice in NPSLE manifestations is magnetic resonance imaging (MRI), which is usually normal in lupus psychosis or has nonspecific findings such as hyperintense lesions, atrophy, or diffuse involvement of the white matter (2, 8). Unfortunately, MRI is not always available, so key clinical findings, and other paraclinical, and neuroimaging findings become important diagnostic aids.

The treatment of patients with lupus psychosis also depends on the presence and severity of other disease manifestations and not only on the psychotic event itself (1). In our patients, a multidisciplinary team defined the management approach. Glucocorticoids are the cornerstone in the induction phase of treatment in lupus psychosis, along with an additional immunosuppressive agent (cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil) which varies widely, as reported by other authors (2, 9). However, EULAR recommends the combination of glucocorticoids and immunosuppressive therapy (usually cyclophosphamide, followed by maintenance with azathioprine) in generalized SLE activity, which results in a significant improvement (60-80% response) (4).

The antipsychotic drug should be chosen based on its efficacy and safety profile. Some authors have proposed olanzapine due to the lower occurrence of extrapyramidal symptoms, according to the evidence in patients with chronic schizophrenia (16, 17). The addition of other psychotropic medications should be considered based on concomitant neuropsychiatric manifestations such as depression or anxiety. Once treatment is established, lupus psychosis has favorable outcomes (1, 2), as described in our patients. It has been described that

more than 80% of the psychotic events resolve by the second annual assessment following the onset of the event (1).
The retrospective nature of our study and the small number of patients included are the main limitations in interpreting and comparing our results with those reported so far in the literature. However, given the gaps in knowledge that persist regarding NPSLE manifestations, the present results can contribute to the existing scientific literature, even more so when only the Latin American population is considered.

CONCLUSIONS

Lupus psychosis is a rare event that usually occurs early in the disease and is associated with high lupus activity. The diagnosis should be made after a thorough exclusion process, in which other causes of neuropsychiatric alterations are ruled out, and should be based on the previously described attribution models. This investigation mainly found concomitant cutaneous, articular, and hematologic involvement, with favorable outcomes after treatment, as described in the literature. Available biomarkers are needed to help support the causal association between SLE and psychosis in clinical practice. As our pathophysiological and clinical understanding of lupus psychosis improves, we could act accordingly from the pharmacological point of view and improve the outcomes of SLE patients.

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