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ORIGINAL ARTICLE

Depressive disorder in Mexican pediatric patients with systemic lupus erythematosus (SLE)

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Abstract

Objective: *To identify the prevalence of depression in Mexican pediatric patients with systemic lupus erythematosus.* **Materials and Methods:** *Analytical transversal study including patients aged 7-16 years with a diagnosis of systemic lupus erythematosus seen at the Pediatric Rheumatology Consultation Service.The disease was classified by means of the MEX-SLEDAI questionnaire. Descriptive statistics with central tendency and dispersion and comparative measurements with chi-squared and Mann-Whitney U tests. Logistic regression and association with odds ratios. SPSS v.21.0 statistical software package.* **Results:** *We evaluated 45 patients who presented depression, n = 9 (20%), including eight females (89%) and one male (11%), median age 13 years (range, 7-16) in children with depression vs. 13 years (range, 9-14) p = 0.941, depression more frequent in schoolchildren. Habitual residence, disease evolution time, and duration of the immunosuppressor did not show a significant difference between both groups. Divorced parents p = 0.037. Neuropsychiatric manifestations of lupus presented in 2.2% of all patients and in 100% of patients with depression. Disease activity index (MEX-SLEDAI) did not demonstrate a relationship with the presence of depression.* **Conclusion:** *Prevalences in pediatric populations are less that that reported in adults, association with disease activity, evolution time, and immunosuppressor use and duration not found.* (Gac Med Mex. 2016;152:30-5)

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune multi-systemic disease with large variability on its presentation and clinical evolution in children and adolescents[1]. Worldwide, an incidence of 0.3-0.9 cases for each 100,000 children/year and a prevalence of 3.3-8.8 for each 100,000 minors are reported[2]. The determination of the degree or intensity of the disease at a given moment establishes therapeutic criteria and on the long-term identifies the degree of progressive damage the patient has experienced. There are several indices to assess the disease activity, such as the MEX-SLEDAI, the Mexican variant of the SLEDAI, developed for emerging countries, which doesn't consider

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some variables, such as the anti-DNA, the serum complement, visual disturbances, lupus headache or pyuria, but highlights proteinuria and includes creatinine > 5 mg/dl, which allow for the variation of manifestations to be assessed (onset, increase, decrease or disappearance), and provide therapeutic recommendations[3].

The manifestations at the central nervous system (CNS) level are one of the main sources of morbidity and mortality in pediatric patients with SLE. Neuropsychiatric (NP) systemic lupus erythematosus (NPSLE) affects both central and peripheral nervous system, with the latter less frequently in children. The prevalence of NPSLE has been reported to range from 20 to 95% in different cohorts; this broad variation in incidence rates has been attributed to the lack of standard definitions of pediatric-age lupus[4].

Usually, more than 50% of the patients with SLE show neurological and psychiatric disturbances indicating a CNS condition; these disturbances are varied and include major manifestations, such as convulsions or psychotic episodes, or less severe such as headaches, mood disorders and cognitive impairments[5].

Depression is one of the most common NP manifestations in patients with SLE, with prevalence reported in different series ranging from 20% to more than 50%. It has been established that children and adolescents with rheumatic conditions have twice as much risk for the development of psychiatric problems than their healthy peers, especially depression, anxiety, general distress and behavioral problems[6].

A chronic disease constitutes a new condition that requires a complicated and active adaptation process, and it is concluded that the child's adaptation to disease is a complex function involving biomedical, evolutionary, behavioral and psychosocial processes. Children and adolescents who suffer from chronic diseases are more likely to develop disorders or problems of the behavioral, social or emotional type[7].

The purpose of this study was to identify the prevalence and characteristics of depression in Mexican pediatric patients with SLE.

Material and methods

Cross-sectional, comparative study carried out from January to December 2013 at the Pediatrics Hospital High Specialty Medical Unit (UMAE – *Unidad Médica de Alta Especialidad*) of the Centro Médico Nacional de Occidente of the IMSS, a reference hospital in the west of the country. The degree of depression, age, gender, family history of depression and marital status of the parents were assessed, as well as characteristics of the disease, such as SLE activity and treatment.

Selection criteria

Patients of the pediatric rheumatology hospitalization and outpatient care areas with a SLE diagnosis according to the American College of Rheumatology criteria of 1982, with ages ranging from 7 to 16 years, with complete medical files, and who knew how to read and write were included. Those patients with a previous diagnosis of any mood disorder other than depression, those with any other physical, neurological or psychiatric condition that hindered the performance of the study and those unwilling to participate were excluded from the study.

Sample size calculation

No sample size calculation was made, since the entire population of the pediatric patients unit with SLE who accepted to participate was included.

Assessment instrument

For the depressive state diagnosis in pediatric patients, the instrument known as the Birleson scale, designed to quantify the severity of depressive symptoms in children and adolescents, was applied. This scale comprises 18 items, with a maximum score of 36 points. It is self-applicable, i.e., the patient can answer by himself, but it also can be read by the healthcare professional in order for the patient to gradually answer. The result is interpreted as follows: 14-20 points: mild depression; 21-27 points: moderate depression; 20 points or more: severe depression.

The SLE activity index was applied using the MEX-SLEDAI, an instrument validated for the Mexican population, which considers a MEX-SLEDAI score > 9 to be active lupus and MEX-SLEDAI < 9 to be inactive disease.

Procedures

The patients were approached in the outpatient care, outpatient chemotherapy, hospitalization and emergency areas where, after an explanation on the purpose of the study and instructions to fill the form, and once the patient accepted to participate in the study, the Birleson scale was applied by the main investigator at the specific area of care of each patient.

Demographics (age, sex, marital status of the parents at the moment of the study, level of education, academic grade point average in the last completed school year, place of residence), as well as information obtained from the electronic and/or physical medical files on intervening variables of interest (time of evolution of the disease, NP manifestations other than depression, mucocutaneous involvement, renal involvement, hematological involvement, cardiac involvement and immunosuppressive treatment at the time of the study), were recorded.

Statistical analysis

Qualitative variables were analyzed by means of frequencies and percentages, and quantitative variables, with medians and ranges (maximum and minimum). The comparison of proportions was performed with the chi-square test, and the medians were compared with Mann-Whitney's U-test. A bivariate analysis was performed to compare the characteristics of each one of the study variables between patients with and without depression, and the association was determined with the odds ratio (OR). A logistic regression model was constructed, with the presence or not of depression as the independent variable and the disease activity index of the disease as independent variable; in addition, adjustments were made for age, sex, time of evolution of the disease (SLE), NP manifestations other than depression, mucocutaneous involvement, renal involvement, hematological involvement, cardiac involvement, immunosuppressive treatment at the time of the study, marital status of the parents at the moment of the study, level of education, academic grade point average in the last completed school year and place of residence. The statistical software SPSS version 21.0 was used to analyze the information. Confidence intervals (CI) were calculated at 95% and a p-value < 0.05 was considered indicative of statistical significance.

Ethical considerations

The study was conducted in compliance with ethical regulations, the Regulations of the General Statute of Heath in Matters of Research for Health, the good clinical practice guidelines and the Declaration of Helsinki. Based on the Belmont Report, verbal consent was requested from the minor as well as written authorization from the parent o legal guardian to apply the Birleson questionnaire. The study was classified as free of risk, and strict confidentiality and anonymity of the patients were preserved. The patients with NP involvement were referred to the Pedopsychiatry Department for follow-up. The protocol was approved by the Local Research and Ethics Committee 1302 of the hospital, with registry number R-2012-1302.

Results

Our study included a total of 45 SLE-diagnosed patients, out of which n = 40 (89%) were females and n = 5 (11%) males. A prevalence of depression of 20% was reported (9 patients: 8 females [18%] and 1 male [2%]).

The depression of the 9 patients identified with the condition was classified as mild (14-21 score) in 8 cases and moderate (22-27 score) in one; no patients had severe depression according to the results on the Birleson scale.

The main sociodemographic characteristics of the patients included in the study and their association with the presence of depression are shown in table 1. A predominance of the female sex, in adolescents, with married parents and residing in the State of Jalisco is observed, with similar frequencies when patients with depression are compared with those without it.

An analysis was performed to identify the relationship between the course of the disease (SLE) and the presence of depression. Table 2 shows the SLE time of evolution (months) in patients with and without depressive disorder at either of its 3 severity degrees, with no significant difference being found (p = 0.261).

The frequency of multi-organ involvement was recorded in all patients with SLE (Table 3) and its relationship with the presence of depression was analyzed, as well as the main manifestations of multi-organ involvement; renal, neurological, musculoskeletal and hematological involvement were the most common in both groups, with significant difference only in the case of presence of gastrointestinal involvement in 4 patients (p = 0.021).

Of the 45 assessed patients, 28 (62%) had at least one of the 19 NP manifestations referred by the American College of Rheumatology as nomenclature for the definition of NP lupus. All patients with depression showed some NPSLE manifestation, whereas 52% (n = 19) of those without depressive disorder exhibited NP manifestations, with a p-value of 0.009. Of the 19 clinical characteristics for NPSLE, headache was the most common with 51% (n = 23), and was present in all 9 patients with depression (100%) and in 14 of the 36 patients without depression (39%), with a p-value

Table 1. Clinical and sociodemographic characteristics of the pediatric patients with SLE according to the presentation group, with or without depression*

	With depression (n = 9)	Without depression (n = 36)	p-value
Female sex, n (%)	8 (18)	32 (71)	0.546
Age in years, median (range	13 (7-16)	13 (9-14)	0.941
Education level (%)			0.986
Primary school	3 (33)	13 (36)	
Middle school	4 (45)	15 (42)	
High-school	2 (22)	8 (22)	
Parents' marital status, n (%)			0.272
Married	6 (67)	26 (72)	
Single	–	2 (6)	
Divorced	3 (33)	3 (8)	0.04
Other	–	5 (4)	
Residence, n (%)			0.227
Jalisco	5 (56)	24 (67)	
Michoacán	1 (11)	5 (14)	
Other State	3 (33)	7 (19)	

*Difference of proportions with the chi-square test; difference of medians with Mann-Whitney's U-test.

Table 2. Relationship of time of evolution of the disease (SLE) with the duration of immunosuppressive treatment in pediatric patients with and without depression*

	With depression (n = 9)	Without depression (n = 36)	p-value
Evolution (months), median (range)	36 (6-72)	24 (1-70)	0.261
Immunosuppressant, (months), median (range)	36 (5-72)	24 (0.70)	0.261
SLE activity according to MEX-SLEDAI			0.393
With lupus activity, n (%)	3 (33)	7 (19)	
Without lupus activity, n (%)	6 (67)	29 (81)	

*Difference of proportions with the chi-square test; difference of medians with Mann-Whitney´s U-test.

Table 3. Relationship between the presence of depression and type of multi-organ involvement in SLE-bearing pediatric patients

	With depression (n = 9)	Without depression (n = 36)	p-value
Multi-organ involvement, n (%)			
Mucocutaneous	2 (22)	3 (8)	0.258
Renal	5 (56)	30 (83)	0.093
Hematological	2 (22)	4 (11)	0.583
Cardiac	1 (11)	3 (8)	1.000
Gastrointestinal	3 (33)	1 (3)	0.021
Musculoskeletal	2 (22)	5 (14)	0.614
Pulmonary	0	3 (8)	1.000
Neurological	3 (33)	6 (17)	0.354

*Difference of proportions with the chi-square test.

Table 4. Main NP manifestations in pediatric patients with NPSLE*

	With depression (n = 9)	Without depression (n = 36)	p-value
NPSLE manifestations, n (%)	9 (100)	19 (53)	0.009
Headache (including migraine)	9 (100)	14 (39)	0.001
Convulsive disorder	3 (33)	7 (19)	0.393
Mononeuropathy	1 (11)	1 (3)	0.278

*Difference of proportions with the chi-square test.

of 0.001. Only 2 patients, one of each group, had other manifestations, specifically mononeuropathy. No patients experienced aseptic meningitis, cerebrovascular disease, demyelinating syndrome, chorea, myelopathy, acute confusional state, anxiety disorders, cognitive impairment, psychosis, mood disorder, demyelinating polyradiculopathy, myasthenia gravis, cranial neuropathy or plexopathy (Table 4).

The logistic regression was carried out with the presence or not of depression as dependent variable, and an adjustment was made for all intervening variables of interest (age, sex, parents' marital status, disease activity and multi-organ involvement). The results are shown in table 5.

Table 5. Logistic regression model of variables in pediatric patients with depression

Variable	p-value	OR (95% CI)
Female sex	0.553	1 (0.09-10.21)
Renal involvement	0.568	1.5 (0.36-6.09)
Neurological involvement	0.263	2.5 (0.48-12.8)
Gastrointestinal involvement	0.023	26.3 (1.5-44.5)
Divorced parents	0.040	12.4 (1.1-133)
Disease activity (MEX-SLEDAI)	0.381	2.5 (0.31-21)

Discussion

Mental disorders are considered a health problem world-wide. Estimates indicate that, by the year of 2020, depression will occupy the second place as disabling condition, the first in developed countries. It affects an average of 15% of the general population, so that, according to estimates, 20% of children and adolescents of the world suffer from some mental illness[8].

In our study, using the Birleson depression scale in SLE-diagnosed children and adolescents, a prevalence of depressive disorder of 20% was reported, which is a figure lower than that estimated for the adult population with SLE (44%), but similar to that reported by D. M. Levy in 2013, who found a prevalence of 26% of depressive symptoms in children and adolescents with SLE. With regard to distribution by sex, it is consistent with reports in the literature, with predominance of the female sex (89%).

We did not find any significant differences between the groups of patients with and without depression with regard to the time of evolution of the disease and immunosuppressive treatment duration, just as in previous series by Ortega-Álvarez, Arias and Harel, who mentioned that even the patients who had not been specifically treated with corticosteroids could exhibit psychosis and depression as the main sign prior to the diagnosis of SLE, as well as some other NP manifestation, thus making it hard to imply these drugs as their cause; actually, some patients improve their function once they are treated with corticosteroids[9-11].

With regard to multi-organ involvement and its relationship with the presence of depression, a significant association was only found with GI involvement, which could be explained as a somatic manifestation of the depressive disorder, since GI complaints are among the main somatic manifestations of depression in children and adolescents, as reported in the *Clinical practice guideline for major depression in childhood and adolescence*[12].

Of the 45 assessed patients, 62% showed some NP manifestation, which was reported in 100% of the patients with depression and in 52% of patients without depression, with a p-value of 0.009, indicative of statistical significance. The most common manifestation was headache in 51% of the total sample and in 100% of patients with depression, followed by convulsive

disorders, with 22%, and with higher prevalence also in the group with depression, but with no statistically significant difference between both groups. This result is above the figure reported exclusively for population pediatric, where the prevalence ranges from 20 to 25%, and is consistent with the higher prevalence of headache, followed by convulsive disorder as the main NP manifestations in both pediatric and adult patients with SLE and depression[9,11,13].

With regard to disease activity, the logistic regression model shows a 2.5 OR, which means that patients with higher disease activity are 2.5 times more likely to have depression; however, there is no statistically significant difference and the confidence intervals are wide.

The parents' marital status has an OR = 12, i.e., children with SLE of divorced parents are 12 times more likely to have depression than children of non-divorced parents, with a statistically significant difference. Finally, GI manifestations have an OR = 26, i.e., children with GI manifestations are 26 times more likely to have depression than children without them, which is consistent with reports in the literature, where no association has been found between disease activity and the presence of NP manifestations, including depression[14,15].

In general, the prevalence of depression in patients with autoimmune conditions reaches significant figures, and the incidence of mental disorders, such as depression and anxiety, has been found not to be related with age, gender, SLE duration or glucocorticoids or cytotoxic drugs doses, but rather with comorbidities such as atherosclerosis, myocardial infarction and antiphospholipid syndrome, among others. This way, depression plays a significant role in the health status of patients with SLE. The relationship and the mechanism whereby depression is produced in SLE are controversial, but life's negative events, disease activity and treatment are known to be able to contribute to its development. Furthermore, as previously mentioned, depression can be the first manifestation of SLE in some cases; on the other hand, it can be the cause of treatment adherence problems that affect the course of the disease.

Conflict of interests

The study has no conflicts of interests.

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