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Prolactin as a Marker of Active Disease in Systemic Lupus Erythematosus

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Abstract: *Objetives.* To determine the correlation between prolactin levels and disease activity classified based on the Mexican lupus erythematosus disease systemic activity index (MEX SLEDAI). *Methods.* In this cross-sectional observational study, serum prolactin, age, sex, treatment, as well as manifestations of active disease were determined. Disease activity was evaluated using the Mexican Systemic Lupus Erythematosus Activity Index (MEX-SLEDAI). The correlation of MEX-SLEDAI with prolactin was determined using the Spearman correlation coefficient. The significance of differences between continuous variables was determined with the non-paired Student's t test and the significance of differences between categorical variables was determined with Chi-square test. *Results.* 55 patients were included, 10 (18.1%) had MEX-SLEDAI ≥7 and 45 (81.8%) less than 7. A positive correlation was found with a Spearman rho 0.387 (p = 0.004) between the MEX-SLEDAI and the levels serum prolactin. Subjects with active disease and hyperprolactinemia had 80% manifestations at the renal level (p = 0.001). *Conclusion.* There is significant correlation between prolactin levels and disease activity. Hyperprolactinemia were detected in patients with renal activity as well as those with MEX-SLEDAI ≥7.

Keywords: Systemic Lupus Erythematosus, MEX-SLEDAI, Prolactin

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune, acute and chronic inflammatory rheumatic disease known for its female predilection and its peak incidence during the reproductive years is of unclear etiology characterized by the production of autoantibodies and systemic manifestations. Mild or moderate hyperprolactinemia has been demonstrated in 20% to 30% of patients with Systemic Lupus Erythematosus (SLE), particularly in those patients with active disease [1].

The higher proportion of women with SLE suggests that sexual factors modulate the propensity and development of the disease [1]. Substantial evidence for the immunoregulatory actions of prolactin (PRL) supports the concept that sex hormones modulate the incidence and severity of disease in patients with SLE [2].

Prolactin is a polypeptide hormone that consists of 199 amino acids and has a molecular weight of 23 kD (kilodalton), with a heterogeneous function, it has a recognized immunostimulatory effect, especially inhibiting the negative selection of autoreactive B lymphocytes, promoting autoimmunity [3, 4].

Patients with active disease have significantly higher serum PRL levels compared to inactive patients. A significant correlation is observed between the serum level of PRL and the concentration of anti-double-stranded DNA antibodies. Patients with high PRL present with active lupus nephritis, as well as fatigue or fever, for which the serum levels of PRL are correlated with the clinical and serological activity of the disease. PRL is considered a perpetual factor in inflammation [5].

This study sets out to use cross-sectional data to determine the relationship between SLE disease activity with PRL levels.

2. Method

It is an observational, cross-sectional, analytical, prospective study conducted in a Mexican hospital "Centro Médico Nacional del Noreste" in June–August 2020. Inclusion criteria were age over 18, female gender, consultant diagnosis of SLE. Exclusion criteria were endocrinopathies, medication that alters the levels of prolactin, creatinine> 2 mg/dl, pregnancy, lactation, psychiatric illness as well as patients who did not sign the consent.

This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee at the Hospital de Especialidades No. 25, Centro Médico Nacional del Noreste. Written informed consents were obtained before entering the study.

Once the consent was signed, the disease activity index was determined using MEX-SLEDAI which evaluates manifestations at the cutaneous, musculoskeletal, renal, neurological and hematological level, measured and recorded by the treating clinician. Those patients with active disease cataloged with MEX-SLEDAI ≥ 7 and those with non-active disease with a MEX-SLEDAI <7 were determined [6].

An serum prolactin collected within of clinician assessment was required. Hyperprolactinemia was defined as PRL levels ≥ 20 ng/ml [7].

The patient age, comorbidities, manifestations of the disease, biological/conventional synthetic disease-modifying antirheumatic drugs (DMARDs) and the use of prednisolone, they were categorised according to active or non-active disease.

Statistical analysis was performed using SPSS software, version 25. Baseline demographics were presented using descriptive methods with median and range. Relationships between dependent and independent variable were tested using Spearman correlation coefficient and represented graphically by scatter graph. The significance of differences between active disease and non-active disease, incorporating all MEX-SLEDAI components, use of DMARDs/biologics/steroids, age, prolactin and comorbidities was determined with the non-paired Student's and the significance of differences between categorical variables was determined with Chi-square test.

Ethical approval information. This study was approved by Institutional board on research ethics, Hospital de Especialidades No. 25, Centro Médico Nacional del Noreste, approval number R-2020-1901-079 (07/16/2020).

3. Results

A total of 55 patients with Systemic Lupus Erythematosus (SLE) between June 1 and August 31, 2020, 50 patients were included in the Rheumatology consultation and five were hospitalized. All patients were women, 10 (18.1%) had a MEX-SLEDAI ≥7 and 45 (81.8%) less than 7. A difference was found in the age of the patients, those with the highest SLEDAI were younger, this was 30 (21-47) vs 40 (18-72) years, respectively. A difference was found in the time of the SLE duration, which was 2.5 (1-16) years for the group with SLEDAI ≥7 compared to 7 (1-24) years for the group less than 7.

Renal disease was the most frequently found clinical manifestation of SLE (14.5%), and when comparing the frequency of these between the 2 groups, kidney disease was more frequent in patients with MEX-SLEDAI ≥7 than in those with lower MEX SLEDAI (80% vs 0%; p = 0.001). No differences were found in the frequency of joint and skin involvement, hemolytic anemia, thrombocytopenia, or neurological involvement.

When comparing the presence of autoimmune diseases associated with SLE such as antiphospholipid antibody syndrome (APS), Sjögren's syndrome, interstitial lung disease, autoimmune hepatitis and fibromyalgia, there were no differences between groups. No differences were found in no other comorbidities associated with SLE *(Table 1)*.

Drug therapy

Regarding immunosuppressive therapy to treat the disease, the use of chloroquine (58.2%) was more frequent, followed by mycophenolic acid (52.7%), azathioprine (29%), tacrolimus (18.2) among others; only 4 (7.3%) patients received biological therapy and there were no differences in drug use between the 2 groups.

The use of steroid was very frequent in all patients (90.9%) regardless of the value of MEX-SLEDAI; all patients (100%) with MEX-SLEDAI ≥7 were taking steroids, compared with 88.9% of those with MEX-SLEDAI less than 7 (p = 0.351) *(Table 2)*.

Prolactin and disease activity.

Hyperprolactinemia was found in 18 patients (32.7%) and this was more frequent in the group with MEX-SLEDAI ≥ 7 (7 patients: 70% vs 11 patients: 24.4%, p = 0.010). There was a difference in serum prolactin levels between the groups, reporting 21 (13-33) ng/ml vs 12 (5-79) ng/ml respectively (p = 0.043).

The median of MEX-SLEDAI was 7 (7-10) for the group with greater activity and 1 (0-5) for the group with less activity. The correlation of disease activity was evaluated using the MEX-SLEDAI score and serum prolactin levels in the 55 patients with SLE, finding a significant correlation with a Spearman Rho of 0.387 (p = 0.004) *(Figure 1)*.

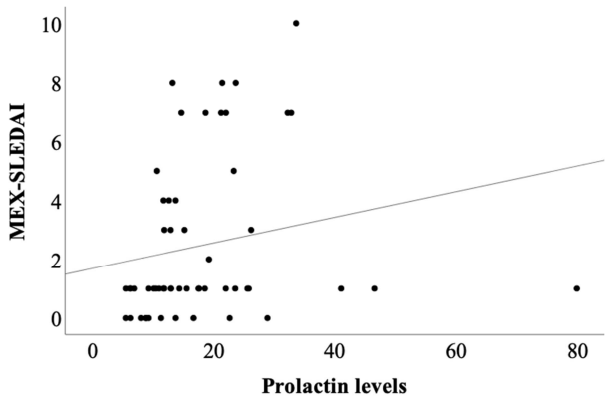

Figure 1. *Scattered diagram shows correlation between prolactin levels and disease activity.*

Table 1. *Clinical characteristics of 55 patients with Systemic Lupus Erythematosus classified based on MEX-SLEDAI.*

	Total (n=55)	MEX-SLEDAI ≥7 (n=10)	MEX-SLEDAI<7 (n=45)	*p*
Age (years), median (range)	40 (18-72)	30 (21-47)	40 (18-72)	0.037
SLE duration (years), median (range)	7 (1-24)	2.5 (1-16)	7 (1-24)	0.088
Clinical manifestations				
Arthritis, n (%)	3 (5.5%)	1 (10%)	2 (4.4%)	0.459
Cutaneous, n (%)	6 (10.9%)	2 (20%)	4 (8.9%)	0.298
Hemolytic anemia, n (%)	2 (3.6%)	1 (10%)	1 (2.2%)	0.333
Thrombocytopenia, n (%)	5 (9.1%)	1 (10%)	4 (8.9%)	0.649
Renal, n (%)	8 (14.5%)	8 (80%)	-	0.001
Neurological, n (%)	1 (1.8%)	1 (10%)	-	0.182
Comorbidities				
Antiphospholipid syndrome, n (%)	10 (18.2%)	2 (20%)	8 (17.8%)	0.588
Sjögren, n (%)	1 (1.8%)	-	1 (2.2%)	0.818
Lung disease, n (%)	1 (1.8%)	-	1 (2.2%)	0.818
Autoimmune hepatitis, n (%)	1 (1.8%)	-	1 (2.2%)	0.818
Fibromyalgia, n (%)	1 (1.8%)	-	1 (2.2%)	0.818
Mellitus diabetes, n (%)	3 (5.5%)	-	3 (6.7%)	0.541
Arterial hypertension, n (%)	18 (32.7%)	3 (30%)	15 (33.3%)	0.578

Table 2. *Treatment and prolactin levels in 55 patients with Systemic Lupus Erythematosus classified based on MEX-SLEDAI.*

	Total (n=55)	MEX-SLEDAI ≥7 (n=10)	MEX-SLEDAI<7 (n=45)	*p*
Drug therapy				
Mycophenolic, n (%)	29 (52.7%)	7 (70%)	22 (48.9%)	0.196
Tacrolimus, n (%)	10 (18.2%)	3 (30%)	7 (15.6%)	0.256
Chloroquine, n (%)	32 (58.2%)	5 (50%)	27 (60%)	0.407
Azathioprine, n (%)	16 (29.1%)	2 (20%)	14 (31.1%)	0.390
Methotrexate, n (%)	8 (14.5%)	2 (20%)	6 (13.3%)	0.450
Cyclosporine, n (%)	9 (16.4%)	1 (10%)	8 (17.8%)	0.478
Leflunomide, n (%)	3 (5.5%)	-	3 (6.7%)	0.541
Rituximab, n (%)	4 (7.3%)	1 (10%)	3 (6.7%)	0.563
Steroid, n (%)	50 (90.9%)	10 (100%)	40 (88.9%)	0.351
MEX-SLEDAI, median (range)	1 (0-10)	7 (7-10)	1 (0-5)	0.001
High prolactin, n (%)	18 (32.7%)	7 (70%)	11 (24.4%)	0.010
Prolactin levels (ng/ml), median (range)	14 (5-79)	21 (13-33)	12 (5-79)	0.043

4. Discussion

The results of this study showed that the majority of patients with active disease had elevated prolactin levels (70%). Vera [8] demonstrated the same results, the relationship between disease activity and the presence of hyperprolactinemia, however the population with active disease was less representative in this study.

The prolactin levels found in active disease, a median of 21 ng/ml was obtained. Jara [9] found prolactin levels> 20 ng/ml in those with active clinical disease as well as serological activity.

Of the clinical manifestations included in the MEX-SLEDAI, a higher prevalence of kidney disease (80%) was demonstrated in those with active disease and hyperprolactinemia. A. Capo [10] found that the presence of hyperprolactinemia was statistically significant in active lupus nephritis (p = 0.014). There was also a positive correlation between prolactin level and score of disease activity (SLEDAI) based on Spearman's correlation coefficient. Therefore hyperprolactinemia is involved in lupus nephritis, activity at the level of the central nervous system, and skin and joint manifestations [11].

Age difference was found in those patients with active disease (p = 0.037), these being younger compared to those with non-active disease, this could be explained by the pathophysiology of the disease since it has a maximum incidence during the reproductive years due to the highest proportion of women with SLE of reproductive age.

Prolactin causes an increase in the binding activity of transcription factors, nuclear factor kappa B, and interferon regulatory factor 1 (IRF1), which are known to promote the secretion of IL 12 and TNF alpha. These data suggest that PRL promotes pro-inflammatory immune responses through NF Kappa B and IRF1 [12].

The expression and synthesis of prolactin has been demonstrated in thymocytes, T cells, B cells and monocytes, the PRL receptor is expressed in both lymphocytes and monocytes, which suggests that the hormone can act in an autocrine or paracrine way, in a similar to cytokines [12]. So, in an active state, high levels of pro-inflammatory cytokines (IL-6) could activate the pituitary to produce excessive amounts of PRL [13].

Several clinical and laboratory indices have been proposed to assess disease activity. One of the strategies to score activity is the use of the systemic activity index of lupus erythematosus disease (SLEDAI), the application of this index can be difficult worldwide. For example, complement determination and other immunological tests are not widely

available, these reasons were taken into account when developing a new instrument, the MEX SLEDAI, a scale that we used in the population of this study due to the characteristics of our population this represents represents one of the strengths of this study since it is easy to apply, another strength is the usefulness of identifying hyperprolactinemia as a marker of active lupus is to carry out actions that slow its progression using it as a tool to identify those patients with active disease being a accessible laboratory in our center.

The most important limitation of this study was that due to the health contingency a greater number of patients was not reached, because the patients did not show up for their medical consultation or the control laboratory studies were not carried out. An important area of opportunity would be the continuity or extension of the study in months after the pandemic to reach a representative sample of patients with lupus and thus have a greater possibility of detecting patients with active disease, since the study of prolactin in the population with Active SLE could have a great impact on treatment and timely evaluation.

5. Conclusion

In conclusion, prolactin can act as a sensitive biomarker of disease activity since a correlation between the two was demonstrated, especially those with active disease established by MEX-SLEDAI, as well as its involvement in lupus nephritis. In patients with SLE it is necessary to classify them as active or non-active disease using any of the validated scales, taking prolactin should be part of routine care, due to its relationship with disease activity.

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