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Can Infection by Sars-Cov2 Induce Systemic Lupus Erythematosus Reactivation?

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is an autoimmune chronic multi-organic disease characterized by a deregulated innate and adaptive response. A series of viral and bacterial agents have been associated with SLE activation. Coronavirus family represents important infectious pathogens in both humans and animals, being responsible for approximately one third of community acquired superior respiratory tract infections. At the end of 2019, a new coronavirus (SARS-CoV-2) was detected as responsible for the COVID-19 disease. It was decided to evaluate if SLE patients had a greater risk of lupus activation when contracting COVID-19.

Material & Method: Sixty two COVID-19 infected SLE patients were studied, comparing those who had suffered lupus reactivation versus those who had not. Renal function, autoinmunity and inflammation markers, and SLE reactivation risk was compared between both groups.

Result: COVID-19 infection in SLE patients did not elevate lupus reactivation risk: OR: 0.8 (0.3-2.6), p: 0.7.

Conclusion: COVID-19 is not, at the moment and as documented, a risk factor for SLE reactivation.

KEYWORDS: systemic Lupus erythematosus, activation, covid-19

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INTRODUCTION

The Latin word “lupus”, which literally means “wolf”, has been presented in medical literature since before the year 1200 (AC), and was utilized to describe lupus skin lesions, and evoked those product of the bite of a wolf (1). Systemic Lupus Erythematosus (SLE) is an autoimmune chronic multi-organic disease characterized by a deregulated innate and adaptive response (2,3). The abnormal activation of the immune system in SLE is distinguished by an excessive B and T lymphocytes activation, as well as a loss of immune tolerance against auto antigens. The clinical manifestations of this pathology are the result of many altered factors, such as the imbalance between production and elimination of antibodies, circulation and immune complex tissue deposits, and complement and cytokine activation. Said manifestations can vary from mild fatigue and arthralgia, to severe organic damage that puts life at risk (4). SLE frequently presents renal damage (up to 75%, according to the series), presenting mainly with glomerulopathy. The presence of proteinuria or an increased proteinuria/creatininuria ratio orientates towards the presence of lupus renal damage, particularly if immune activity signs are present, such as elevated anti deoxyribonucleic acid antibody concentration (anti - ADN) and complement system decrease (5). Incidence rates of SLE have varied all over the world, from approximately 0.3-23.7 of 100.000 people per year (ppy), while prevalence rates have oscillated about 6.5-178.0 of 100.000 ppy (6-9). Even though SLE can appear at any age, it is more common in women than in men, particularly in women in childbearing age (24-32 years). This disease presents characteristically with an 8 to 15:1 proportion of women to

men, while in late onset and prepubertal lupus, the proportion is of 2-8:1. (10) The childhood lupus onset occurs in a more constant way around 12 to 17 years of age, and it represents from 10 to 20% of SLE cases. On the contrary, late lupus onset (which occurs at age ≥ 50), represents 15% of all cases (11). The debut age is determined and influenced by the patient characteristics and their ethnic background. The mean age of appearance in Canadian aborigines is of 34 years, followed by 33 in Caucasians, 30 in Afro-Caribbeans and 25 in Asians. (12) While in Latin America Caucasians represent patients with the oldest mean age of onset, at 29.5 years, then mongrels (mixed European and Amerindian origins), at 28.2, and lastly Afro-Latin Americans at 26.2 years (13). Within incidence and prevalence rates of every ethnic group of SLE, and SLE in general, non-Caucasians count on higher rates than Caucasians. (14) It has been concluded that SLE in mongrels and Afro-Latin Americans presents at a younger age and with higher frequency and severity than in Caucasians. (15) A connection between smoking and specific manifestations of SLE, such as skin lesions, serositis, neuropsychiatric and renal disorders, has been established, particularly with discoid and subcutaneous lupus (SCLE). (16,17). Exposure to xenobiotic products, organic solvents, silica powders, uranium, pesticides (organic and inorganic chemicals), phthalates (organic industrialized chemicals used for plastic manufacture) and cosmetics has been related to SLE. (18,19) Photosensitivity is a clinical criteria of SLE and is present in 30-50% of patients, particularly in those who have positive serology for anti SSA/Ro and/or anti SSB/La antibodies. UV radiation, both ultraviolet- A2 (UVA) and ultraviolet B (UVB), can induce cutaneous manifestations and exacerbate cutaneous and systemic manifestations of preexistent SLE (20). Likewise, there are potentially SLE inducing drugs, such as hydralazine, procainamide, isoniazid, minocycline, diltiazem and TNF inhibitors. (21-23). In the last decade, many studies have analyzed the effects of socio-economic status on SLE activity, discovering that a higher education was associated with a lower SLE activity, while poverty was related with a higher activity and mortality of the disease. (21-23). Finally, infections not only represent a significant contributing factor of morbidity and mortality among SLE patients, but some have also been associated with the development of some autoimmune phenomena, and particularly with lupus reactivation. Coronaviruses represent important infection generating pathogens both in humans and animals, being responsible for approximately one third of community acquired upper respiratory tract infections. Additionally, other gastrointestinal tract and central nervous system infections caused by these viruses have been described. At the end of the year 2019 a new coronavirus accountable for the pneumonia epidemic in Wuhan, China, was identified, which progressively propagated around the world becoming a pandemic.This virus has been named by the world health organization (WHO) as SARS-CoV2, and causes COVID-19, the disease that has infected over 220 million people all around the world (29). Despite being a zoonotic disease, its main propagation means has been interhuman, mostly through respiratory droplets while talking, coughing or sneezing. COVID-19 clinical presentation can oscillate from a paucisymptomatic condition, a pulmonary compromise (pneumonia) followed or not by another vital organ manifestations (acute kidney injury), up to a systemic inflammatory state with a very high mortality rate (cytokine storm) (30-39). It is important to consider that both the patient's comorbidities and risk factors establish the COVID 19 disease life prognosis. It is known that not everyone who suffers some level of immunodeficiency, such as lupus, develops a serious infection by COVID-19, nevertheless they do have a greater risk of contracting it. (40-43). Thus, from observing a series of lupus patients that were hospitalized for COVID-19 who presented a reactivation of its previous disease, we decided to evaluate if SARS-CoV-2 could be directly linked to SLE reactivation.

MATERIAL & METHOD

An observational, descriptive and retrospective study was performed with data obtained from patients diagnosed with COVID-19 (detection by PCR) who were assisted either on the emergency room, general ward, intensive care unit or teleconsultation at Clínica de la Costa, Barranquilla (Colombia). The studied patients were selected following the next inclusion and exclusion criteria:

Inclusion criteria:

- Age ≥ 18 years
- Positive PCR test for COVID-19 diagnosis
- SLE and/or lupus nephropathy diagnosis by renal biopsy
- Signed patient´s informed consent

Exclusión criteria:

- Age < 18 años
- Refusal to let their data be used for investigation

It was initially proceeded to select the patients who met the inclusion-exclusion criteria. Their data was then taken from clinical records, and consisted in: Age, cretininemia, autoimmunity markers (Anti-DNA antibody, antinuclear factor, C3, C4), inflammatory markers (Ferritin, D-dimer). (Table 1).

The statistical data analysis was done by applying the t student test or the Mann-Whitney test, according to the normality or not of its distribution, respectively. Additionally, the Wilcoxon test was used. A value of $p \leq 0.05$ was considered significant.

The study was approved by the Bioethics institutional committee and the informed consent of every participant was included in the study.

RESULTS

In the present study, 64 SLE patients under treatment with a combination of prednisolone 5mg/day, mycophenolate 1500mg/day and hydroxychloroquine 200mg/day were analyzed. The patients were assisted for having contracted COVID-19 (PCR) at Clínica de la Costa (Colombia) during the study period (April-December 2020). From the 64 patients, 40 presented a reactivation of their SLE during the COVID-19 infection, and 24 did not suffer a reactivation. When both groups were compared regarding the evaluated variables, no significant age difference between these was documented (young adults) (Table 1). Nevertheless, a statistically significant difference was in fact documented respecting higher creatininemia (p: 0,011) and autoimmunity markers levels (p:<0.05), elevated inflammatory parameters (p: <0.05), and lower C3 serum levels (p: 0.004) in the reactivated SLE compared to the non-reactivated SLE (Table 1). Finally, by means of logistic regression, it was evaluated if the fact of suffering COVID-19 increased the risk of a SLE reactivation on these patients, obtaining a OR: 0.8 (0.3-2.6), p: 0.7.

DISCUSSION

Some infectious agents have been related with clinical manifestations of autoimmune diseases. Such as Mycobacterium pneumoniae and Klebsiella pneumoniae, which have been associated to anti-DNA antibodies induction, both in humans and animals (27). In regards to viruses, epidemiological studies in humans and animals have demonstrated that these are capable of interacting with the immune system. Thus, they modify how the system acts against its own cells, being able to induce an autoimmune process or exacerbate those already present. The proposed mechanisms are molecular mimicry, unspecified immune system activation and epitope propagation. Molecular mimicry makes reference to the antigenic similarity between some viruses and their own antigens, given by the resemblance on its amino acid chains. Mimicry ends at the antibodies cross reaction, which react so much with the viral antigen as with auto antigens of similar structure or dual TCR (T cell receptor) activity on T lymphocytes. .

As to the nonspecific immune system activation, it is given by innate immune system activation, in this case with a profiling towards antiviral mechanisms which generate a pro-inflammatory state. It is an antigen independent response; however, the pro inflammatory state sensitizes the immune system, increasing its response capacity. Lastly, de epitope propagation refers to the tissue damage caused by viruses, with a consequent autoantigen release. These are then taken by the antigen-presenting cells and subsequently presented to adaptive immunity cells. The auto antigen surplus under a pro-inflammatory nonspecific state in a patient with a low immunity tolerance or previous autoimmunity may culminate with an autoimmune disease debut or the reactivation of an underlying autoimmune disease, as studied in this paper.

As to viral agents, the ones already documented associated with lupus reactivation were Epstein-Barr (VEB), cytomegalovirus (CMV), parvovirus B19, rubella, parotitis (Mumps), retroviruses and other transfusion-transmitted viruses (28).

The coronavirus family possesses a series of structural proteins capable of inducing immune stimulation, and therefore a potential autoimmune reactivation. Between these proteins we must name: S protein (spikes), which gives the virus its typical crown-shaped structure and also mediates its binding to the receptor, via S1 domain, and to the host membrane, via S2 domain (30). The same occurs with other of the virus proteins, such as M protein (membrane), which is essential for the viral assembly; M protein (nucleocapsid) that has regulation capacities for viral RNA production: HE glycoprotein (hemagglutinin-esterase) which is only present in beta coronavirus and binds to neuraminic acids on the host cell surface, allowing the initial adsorption of the virus; and finally, E protein (envelope) (31-33).

In regards to the COVID-19 clinical presentation, it may vary from a mild symptomatology to severe cases that may lead to death. Nevertheless, most cases do not represent a great risk to humans, being severe in 14% of cases and critical in 5% of these (34-36). The critical cases can present at any age group, still, advanced age and comorbidities (cardiovascular disease, diabetes mellitus, hypertension, chronic) pulmonary disease, cancer, chronic kidney disease) are counted as risk factors. Likewise, worst disease outcomes have been described in patients with lymphopenia, elevated hepatic enzymes, elevated LDH, elevated acute phase reactants (C reactive protein and ferritin), elevated D-dimer, prolonged clotting time, elevated troponin and creatinin kinase, as well as in patients who develop acute kidney injury (AKI) (37,38).

Its clinical manifestations are diverse, with worst cases presenting pneumonia with associated fever, coughing, dyspnea and bilateral pulmonary compromise, ventilatory difficulty in 20% of patients and mechanical ventilation needs in 12% of them. Other less frequent complications are arrhythmias, acute myocardial infarction and shock (39,40).

In the present study it was evaluated if SLE exacerbation could be another form of presentation, on one hand given by the immune deployment caused by COVID-19 (cytokine storm), and on the other hand by the underlying immune disorder of these patients, secondary to various factors, such as corticoid treatment, cytotoxics and other immunosuppressants (41-43). Nonetheless, our study has documented that COVID-19 disease did not increase the risk of lupus reactivation: OR: 0.8 (0.3-2.6), p: 0.7

CONCLUSION

The present study documented that COVID-19 does not appear to be a risk factor for systemic lupus erythematosus reactivation.

Compliance with Ethical Standards

CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest. Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.Informed consent: Informed consent was obtained from the patient.

Table 1: Principales variables analizadas

	SLE reactivated	**SLE non- reactivated**	P
Age (years)	34 ± 10	37 ± 12	0.40
Serum creatinine (mg/dl)	1,4 ± 1,36	0,77 ± 0.18	**0,011**
ANA	positive	negative	-
Anti-DNA	positive	negative	-
C3 (mg/dl)	97 ± 23	104 ± 15	**0,004**
C4 (mg/dl)	27 ± 9	28 ± 8	0,52
D-Dimer (ng/ml)	1345 ± 2182	279 ± 142	**0,0005**
Ferritin (Ug/L)	361,4 ± 474,4	138 ± 45	0,067

Systemic lupus erythematosus (SLE), **ANA:** antinuclear antibody, **C**: complement

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