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# Neuropsychiatric damage in Systemic Lupus Erythematosus: Possible protective role of medications.

**Daño neuropsiquiátrico en Lupus Eritematoso Sistémico. Posible papel protector de las medicaciones.**

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## SUMMARY

**Objective:** To examine the possible role of medications in the occurrence of neuropsychiatric damage in patients with systemic lupus erythematosus (SLE). **Material and methods:** SLE patients from the LUMINA (Lupus in Minorities: Nature vs. Nurture) cohort (ACR criteria,  $\geq 16$  years of age at enrollment and  $\leq 5$  years of disease duration) were studied. Time-to-neuropsychiatric damage [defined according with the Systemic Lupus Collaborating Clinics (SLICC) Damage Index (SDI): neurocognitive impairment or psychosis, seizures, cranial or peripheral neuropathy, stroke or surgical resection not due to malignancies and transverse myelitis] was examined by univariable and multivariable Cox regression analyses. Propensity score analyses were done to further determine the possible protective role of hydroxychloroquine in neuropsychiatric damage occurrence. **Results:** Six-hundred and thirty-two patients were studied. Age, Caucasian ethnicity, disease activity over time, diabetes and abnormal illness-related behaviors were associated with a shorter time-to-the occurrence of neuropsychiatric damage whereas photosensitivity, anemia, Raynaud's phenomenon, hydroxychloroquine and a medium dose of prednisone were associated with a longer time. Although the direction of the association remained the same by propensity score analyses (hydroxychloroquine), significance was no longer evident. **Conclusions:** Our data suggest a possible protective role of hydroxychloroquine and moderate doses of prednisone in the occurrence of neuropsychiatric damage in patients with SLE. (*Rev. Neuropsiquiatria* 2008; 71: 51-57).

**KEYWORDS:** Neuropsychiatric damage, SLE, hydroxychloroquine.

## RESUMEN

**Objetivo:** Examinar el posible rol de medicaciones en el desarrollo de daño Neuropsiquiátrico en pacientes con lupus eritematoso sistémico (LES). **Materiales y métodos:** Se incluyeron pacientes con LES (Criterios del ACR,  $\geq 16$  años al momento de ser enrolados en el estudio,  $\leq 5$  años de duración de la enfermedad) de la cohorte LUMINA (Lupus in Minorities: Nature vs. Nurture). El tiempo-a-desarrollar daño neuropsiquiátrico (psicosis o impedimento

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neurocognitivo, convulsiones, neuropatía periférica o craneal, accidente cerebrovascular, mielitis transversa) fue examinado mediante regresiones univariantes y multivariantes de Cox. Además se realizaron análisis de propensión para determinar el posible rol protector de la hidroxiquina en el desarrollo de daño neuropsiquiátrico en estos pacientes. **Resultados:** Se estudiaron 632 pacientes con LES. La edad, etnia caucásica, actividad de enfermedad a lo largo de la misma, diabetes, y conductas anormales relacionadas con la enfermedad estuvieron asociadas con un tiempo más corto para el desarrollo de daño neuropsiquiátrico. Por otro lado la fotosensibilidad, la anemia, el fenómeno de Raynaud, y el uso de hidroxiquina y dosis medias de prednisona estuvieron asociados con un tiempo más prolongado. La dirección de la asociación fue la misma cuando se realizó el análisis de propensión pero la significación estadística se perdió. **Conclusiones:** Nuestros datos sugieren un posible rol protector de la hidroxiquina y de dosis medias de prednisona en el desarrollo de daño neuropsiquiátrico en pacientes con LES. (*Rev. Neuropsiquiatria* 2008; 71: 51-57).

**PALABRAS CLAVE:** Daño neuropsiquiátrico, LES, hidroxiquina.

## INTRODUCTION

Involvement of the central nervous system in systemic lupus erythematosus encompasses a number of different manifestations which vary in their characteristics and severity (1-3). The American College of Rheumatology (ACR) has recognized for many years two of them, seizures and psychosis as criteria for the classification of patients with the disease (4,5); however, many other neuropsychiatric (NP) manifestations occur in lupus. The ACR has recently recognized this diversity and 17 other syndromes have been described; these manifestations, however, do not constitute ACR criteria (6). While some of these syndromes may be transient leaving no permanent sequel or organ damage, others may not as they may be transient and entirely reversible. The SLICC (for Systemic Lupus International Collaborating Clinics) group has included a NP-domain within the SLICC Damage Index or SDI (7). Determining the role of medications in accelerating or retarding the development of NP damage has obvious practical implications to the management of patients afflicted with this disorder. We were particularly interested in examining the role of antimalarials, namely hydroxychloroquine, in NP damage occurrence given their overall beneficial effects in lupus that we and others have demonstrated, namely preventing relapses or flares of the disease (8,9), preventing the occurrence of damage (10,11) and retarding the occurrence of renal (12) and integument damage (13), and exerting a protective effect on lupus survival (14-16).

We have now examined this in a US multi-ethnic cohort of lupus patients established in 1993 to elucidate the discrepant outcomes of lupus among ethnic minorities and the majority population.

## PATIENTS AND METHODS

Briefly, LUMINA (for Lupus in Minorities: Nature vs. Nurture) is a multiethnic cohort of SLE patients established in 1993 in response to a request for applications from the National Institute of Arthritis and Musculoskeletal and Skin Disorders to study the discrepant outcomes of lupus in ethnic minorities and the ethnic majority. Participating centers include The University of Alabama at Birmingham (Birmingham, Alabama), The University of Texas Health Sciences Center at Houston (Houston, Texas), and the University of Puerto Rico Medical Sciences Campus (San Juan, Puerto Rico) (17,18).

Patient recruitment started in 1994, except in Puerto Rico where recruitment did not commence until 2001. Patients had SLE according with the modified and updated ACR classification criteria (4,5), were 16 years or older at enrollment, and had up to 5 years of disease duration. Eligibility was determined by each site investigator after all available medical records had been reviewed. The recruitment visit (T0) included, in addition, an interview, completion of different questionnaires, a physical examination and laboratory tests. Subsequent visits took place every six months for the first year and yearly thereafter. Diagnosis time (TD) is the time at which patients met four ACR criteria and TL is the time of the last available visit. The study followed the guidelines of the Declaration of Helsinki for human research.

NP-damage, the dependent or outcome variable, was defined per the SDI as the presence, for at least six months, of one or more of the following clinical events: cognitive impairment or major psychosis, seizures, cranial or peripheral neuropathy (excluding optic

neuropathy), and transverse myelitis; cerebrovascular accident (CVA) or surgical resection for causes other than malignancy are scored regardless of their duration. A second CVA if occurs more than six months apart from the first is also scored. As per the SDI, these events are defined clinically; thus, no formal neuropsychological testing, imaging or electrophysiological studies are required for a manifestation to be scored in the NP domain of the SDI (7).

Only the variables included in these analyses will be now described. Variables from the socioeconomic-demographic domain included were age, gender, ethnicity, marital status, education, poverty (as defined by the US Federal Government adjusted for the number of subjects in the household) (19), health insurance and health-related behaviors (smoking, drinking and using recreational drugs).

Clinical variables included were disease duration (from TD to T0), disease onset type (acute if in less than four weeks, insidious if otherwise), the number of ACR criteria, non-ACR criteria manifestations [CVA (transient ischemic attack, stroke and subarachnoid hemorrhage), headaches, neuropathy (cranial neuropathy, peripheral neuropathy or mononeuritis multiplex), myelopathy, mood disorder (depression) and cognitive dysfunction], antiphospholipid antibodies (aPL, including IgG and IgM aPL and the lupus anticoagulant), disease activity (ascertained with the Systemic Lupus Activity Measure-Revised or SLAM-R) (20), disease damage [ascertained with the SDI (11 other domains in addition to the NP-domain, all scored on clinical basis) (7), and comorbidities (hypertension, diabetes, and hypercholesterolemia). For both, the SLAM-R and the SDI, total scores were calculated omitting the NP manifestations. Cumulative medication usage was considered up to TL for those patients in whom NP damage did not occur and up to the time NP-damage developed for those in whom it occurred. Glucocorticoid use was defined as a categorical [low (< 10 mg/dl), medium (10-30 mg/day) and high (> 30 mg/day)] and as a continuous variable, as we were interested in examining the possible effect not only of the different glucocorticoid dose categories but also the impact of its continuous use.

Variables from the psychological and behavioral domain included were social support (ascertained with the Interpersonal Support Evaluation List or ISEL) (21), Coping with Illness (ascertained with the Illness Behavior Questionnaire or IBQ) (22) and Helplessness

(ascertained with the Rheumatology Attitude Index) (23).

**Statistical Analyses.** Variables from the different domains between patients who developed NP-damage and those who did not were compared using descriptive statistical tests (Chi-square for proportions and Student's t tests for means). Variables with a p value =0.10 in these analyses were then entered into univariable Cox regression models with time to NP-damage being the dependent variable; those variables with a p =0.10 in these analyses were entered into a multivariable Cox regression model using a backward selection procedure until only variables with p =0.05 were retained in the model. Results were expressed as Hazard Ratios (HR) and their 95% Confidence Intervals (CI). A HR >1 indicates a shorter time to NP-damage occurrence and the opposite if <1. All analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC).

## RESULTS

At the time these analyses were performed there were 632 patients in the LUMINA cohort, 117 (18.5%) were Texan-Hispanics, 102 (16.1%) Puerto Rican-Hispanics, 234 (37.0%) African American and 179 (28.3%) were Caucasian. As expected, the majority of the patients (88.6%) were women; their mean (Standard deviation, SD) age at T0 was 38.6 (12.5) years and their mean disease duration was 18.9 (15.8) months. One hundred and eighty-five patients had developed NP damage at a mean (SD) disease duration of 5.6 (3.7) years; 135 neurocognitive impairment (130.0) or psychosis (5.0), 45 strokes, 30 seizures, 22 cranial or peripheral neuropathy, and 3 transverse myelitis.

**Univariable Analyses.** Texan-Hispanic, African American and Caucasian ethnicities were associated with a shorter time-to-NP damage occurrence as compared to the reference ethnic group (Puerto Rican-Hispanics); likewise, poverty, higher levels of illness-related behaviors and of helplessness were associated with a shorter time-to-the occurrence of NP damage. In contrast, years of education, health insurance and higher levels of social support were associated with a longer time-to-the occurrence of NP damage.

In terms of the clinical variables, in addition to the neurological manifestations (seizures, psychosis, CVA and cognitive disorder), hemolytic anemia, aPL antibodies, hypercholesterolemia, disease activity at TD and T0, damage accrual at T0 but not at TL, diabetes, the weighted average maximum prednisone dose and

prednisone at a dose ( $> 30$  mg/day) were associated with a shorter time to the development of NP damage.

In contrast, disease duration, malar rash, photosensitivity, lymphopenia, Raynaud's phenomenon, hydroxychloroquine use and a medium dose of prednisone ( $>10$ - $30$  mg/day) were associated with a longer time. Other medications were not associated with a high NP damage occurrence (data not shown).

**Multivariable Analyses.** After adjusting for the presence of neuropsychiatric manifestations, older age at T0, Caucasian ethnicity, disease activity over the course of the disease, diabetes and abnormal illness-related behaviors were associated with a shorter time to the occurrence of NP damage. On the other hand, photosensitivity, anemia, Raynaud's phenomenon, a medium dose of prednisone and hydroxychloroquine use were associated with a longer time-to-NP damage occurrence. These data are depicted in table N°1. Removing the five patients in whom psychosis had occurred from this regression did not alter the results of these models (data not shown).

**Propensity Score Analyses.** Given the apparent protective effect of hydroxychloroquine on time to NP-damage, propensity score analyses were performed to adjust for confounding by indication (24-26). In these analyses all variables that differed between hydroxychloroquine takers and non-takers were considered in the derivation of the propensity score; patients with less severe disease had a lower propensity score or a diminished probability of being treated with hydroxychloroquine, and vice versa; this score was then used as the only adjustment variable in a multivariable Cox regression analyses with time to the occurrence of NP damage being the dependent variable. Although the HR for hydroxychloroquine remained below 1 after adjusting for the propensity score, the 95% CI encompassed the unit, and thus statistical significance was not reached. The propensity score, on the other hand, was highly significant (the higher

**Table N°1:** Time-to-Neuropsychiatric Damage Occurrence by Multivariable Cox Proportional Hazards Regression Analyses in LUMINA Patients\*

Variable	Hazard Ratio	95% Confidence Interval	p value
Age at baseline, years	1.02	1.00-1.04	0.0233
Caucasian ethnicity	1.87	1.22-2.87	0.0041
Clinical manifestations			
Photosensitivity	0.65	0.44-0.95	0.0257
Anemia	0.56	0.31-0.98	0.0448
Raynaud's phenomenon	0.49	0.34-0.72	0.0002
Systemic Lupus Activity Measure-			
Revised weighted	1.16	1.12-1.21	<0.0001
Diabetes	3.47	1.44-8.38	0.0056
Medications			
Hydroxychloroquine	0.58	0.36-0.93	0.0248
Glucocorticoid <sup>†</sup> , dose mg/d			
Medium dose (10-30 mg/day)	0.56	0.35-0.92	0.0211
Abnormal coping behaviors <sup>‡</sup>	1.05	1.02-1.08	0.0011

\* Variables in the model are, in addition to the ones shown in Table, the following: gender, ethnicity, education, poverty, malar rash, hemolytic anemia, neuropsychiatric manifestations (seizures, psychosis, cognitive impairment and stroke), damage at T0 (without NP domain items), aPL antibodies, hypercholesterolemia, social support and helplessness; <sup>†</sup>as prednisone equivalent; <sup>‡</sup>per the Illness Behavior Questionnaire.

the score, the higher the HR). These data are depicted in table N°2.

## DISCUSSION

We have shown that NP damage may be retarded by both, the use of hydroxychloroquine and of a medium dose of glucocorticoids in patients with SLE from the LUMINA cohort. The effect of hydroxychloroquine was evident when adjusting for multiple other variables significant in the univariable Cox regressions; however, when features that distinguished hydroxychloroquine takers from non-takers were considered to derive the propensity score or the probability that a patient will take this compound as a function of these features, the HR remained below the unit indicating the persistent protective effect of hydroxychloroquine but the 95% CI encompassed the unit and thus statistical significance was not reached. In terms of glucocorticoids, our data indicate that while a medium dose ( $>10$ - $30$  mg of prednisone or equivalent



per day) retards the occurrence of NP-damage, a lower or higher dose may be detrimental.

Although the protective effect of hydroxychloroquine could not be convincingly demonstrated when the propensity score analyses were performed, it has been recently suggested that multivariable analyses in which all pertinent variables are included are equally adequate (27,28). Of course, the issue of remaining confounding withstands, as it is always possible that using either method to adjust for confounding by indication, or the probability that a given treatment is administered to a patient with specific clinical or sociodemographic characteristics, important characteristics (which may not be obvious to the investigators) are not included in either the derivation of the propensity score or in the multivariable analyses. Given these considerations and the overall anti-inflammatory, anti-thrombotic, anti-platelet, hypolipidemic, glucocorticoid-sparing and immunomodulatory properties of hydroxychloroquine in particular, and of antimalarials in general (29-32), coupled with their relatively benign safety profile and their protective effect on preventing relapses or flares, on overall damage and on integument and renal damage and on survival, as well as their potential protection from serious infections (33), antimalarials should be regarded as important and standard elements of the treatment of patients with lupus (12,15). Needless to say, especially when chloroquine rather than hydroxychloroquine is used, all precautions should be taken to prevent the occurrence of ocular toxicity. Dosing these compounds to the ideal (rather than the actual) body weight, and periodic ophthalmologic evaluations are needed (34).

In terms of the glucocorticoids, although our data suggest that a medium dose is protective, how long this dose should be administered to exert this protective effect could not be determined. It is conceivable that a short course of such a dose is indeed protective and well-tolerated while a prolonged course although potentially beneficial in terms of retarding the occurrence of NP-damage may be detrimental from so many other angles that it cannot possibly be recommended (35-38).

Of all the other factors identified in the multivariable analyses as either protective or deleterious in terms of NP-damage, the only modifiable one is abnormal illness-related behaviors. Modifying the manner in which patients confront their illness goes beyond what most generalists and specialists do on a daily basis, but it is

something to consider in comprehensive interdisciplinary lupus clinics if the outlook of patients with lupus is to improve.

In summary, despite the fact that NP-damage is not an independent predictor of mortality in lupus, efforts should be taken to try to prevent such occurrence as it may have significant impact in the quality of life of these patients. Rational use of medications, including antimalarials and glucocorticoids is highly desirable.

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