



Predictors of damage accrual in systemic lupus erythematosus: a longitudinal observational study with focus on neuropsychological factors and anti-neuronal antibodies

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Abstract

Objective Central nervous system disease occurs in over 20% of patients with systemic lupus erythematosus (SLE) resulting in major morbidity and damage. Cognitive dysfunction is common in SLE, but the cause remains uncertain and treatment options are limited. This study explores the influence of clinical, neuropsychological factors and anti-neuronal antibodies on lupus damage accrual.

Method A prospective cohort with 99 SLE patients recruited between 2008 and 2013 and followed up in 2016 was established. Baseline evaluations were depression (MINI-Plus), cognitive function evaluating attention, visuospatial memory and executive functions, and anti-neuronal antibodies. Activity index (SLEDAI-2K) and SLICC/ACR Damage Index (SDI) were assessed at baseline and last follow-up.

Results At baseline, median (interquartile range) age was 36.0 years (27.0–45.0), disease duration 3.7 years (0.4–12.4), SLEDAI-2K 6.0 (3.0–12.0), and SDI score 1.0 (0–1.0). Major depression was present in 23%, cognitive deficit in 18%, and received immunomodulators in 36%. Anti-dsDNA/N-methyl-D-aspartate receptor antibodies were present in 19%, anti-ribosomal P in 12%, and anti-neuronal surface P antigen (NSPA) in 5%. After a median follow-up of 55 months (interquartile range 39–78), 11% had damage accrual. In a multivariate analysis, baseline SDI, SLEDAI-2K, and immunomodulators use were associated with final damage, whereas SLEDAI-2K and immunomodulator use were also associated with accrual damage. Models including anti-NSPA showed impact on final and accrual damage. Cognitive deficit, depression, and other autoantibodies were not predictors.

Conclusions Disease activity and immunomodulator use associate with lupus damage. Of the anti-neuronal antibodies examined, anti-NSPA emerged as a potential poor prognostic factor, probably related to severe SLE onset requiring elevated corticosteroid doses.

Key Points

- *Anti-NSPA may be a worse prognostic factor in SLE.*
- *Other neuropsychological factors do not influence damage.*

Keywords Damage accrual · Neuropsychological factors · Anti-neuronal antibodies

Indexing terms Systemic lupus erythematosus · Severity of illness index · Neuropsychological tests · Cognitive dysfunction · Autoantibodies

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Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder characterized by the presence of autoantibodies against a variety of antigens. Patients with SLE are at risk of premature death [1] and accumulated damage, frequently involving ocular, musculoskeletal, renal, and neuropsychiatric systems [2, 3].

A single validated tool, the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) is available to measure organ damage [4]. This score increases over time and predicts mortality [2, 3]. Factors associated with the accrual of damage include male gender, older age at SLE onset, longer disease duration, disease activity, higher SDI score at cohort entry, renal disease, and use of corticoids and immunosuppressive drugs [5–8]. Interestingly, antimalarial use has a protective role in damage accumulation [9, 10].

Neuropsychiatric SLE (NPSLE) is associated with SLE damage [2]. According to the applied definition [11], NPSLE reported prevalence ranges from 6–39% up to 80% in patients [12]. Cognitive dysfunction is the most common NPSLE manifestation and is present in 17–66% of patients [13]. An impact of cognitive deficit on damage has been suggested. However, in these cohorts, the cognitive function tests used a low stringent criteria and cognitive impairment varied over time and even improved [14–17]. In contrast with other studies, our previous study applied the Cambridge Neuropsychological Automated Battery (CANTAB) and followed stringent definition criteria of cognitive deficit, revealing cognitive deficit in only 18% of patients studied [18]. CANTAB is sensitive to minor cognitive deficits, and has the advantage of isolating the cognitive domains dependent on the fronto-striatal circuit. Therefore, our cohort seems appropriate to define the role of cognitive dysfunction in lupus damage, a main outcome measure in SLE.

In addition, to our knowledge, there are no reports on the role of anti-neuronal antibodies on damage accrual. Our cohort can provide information to this respect, as we found an association between cognitive deficit and the presence of circulating anti-dsDNA/methyl-D-aspartate receptor (anti-dsDNA/NMDAR) and anti-ribosomal P proteins (anti-P) antibodies [19]. These two antibodies recognize neuronal surface antigens that are distributed in regions involved in memory, cognition, and emotion and have demonstrated neuropathogenic potential [20–22]. The function of NMDAR is well known in glutamatergic transmission associated with neuronal plasticity underlying spatial memory and its dysfunctions are involved in emotional and behavioral disorders [23]. anti-P antibodies, originally associated with lupus psychosis [24], cross-react with a plasma membrane protein of unknown function, called the neuronal surface P antigen (NSPA) [25], which is also involved in neuronal excitatory transmission and mediates anti-P effects on memory dysfunction in mice models [26, 27].

Here, we investigate factors associated with damage in a cohort of 99 SLE patients that completed a thorough neuropsychological assessment along with anti-neuronal antibody measurement at baseline, after 5 years of follow-up. We include data on a new class of antibodies that recognize NSPA lacking anti-P reactivity.

Methods

From our study group of 118 SLE patients recruited between 2008 and 2013 [28], a subset for a longitudinal observational cohort of 99 SLE patients was established and followed up in 2016. No differences between patients that took part in this subset and those who did not have follow-up were found, as shown in Online Resource Supplementary Table 1.

Patients attended the outpatient facilities of the UC-Christus Health Network. Inclusion criteria were as follows: female gender, age older than 16 years, and fulfilling four or more of the American College of Rheumatology (ACR) revised criteria for the classification of SLE [29]. Exclusion criteria were as follows: severe renal failure (creatinine clearance < 10 ml/min), severe infections, mental disability that precluded performing evaluations (delirium assessed by the Confusion Assessment Method Test [30], scores below 70 on the Addenbrooke's Cognitive Examination Revised test [31]), or history of severe mental illness. All patients were able to understand their role in the study and had completed at least primary school.

All participants voluntarily signed an informed consent approved by the Institutional Ethical Committee prior to their inclusion in the study.

Baseline evaluation was performed on one day with a structured protocol, considering healthy pauses to avoid fatigue, and included the following:

1. General data: age, years of education, disease duration since SLE diagnosis, SLE Disease Activity Index 2000 (SLEDAI-2K) [32], SDI [4] according to the definitions outlined in the corresponding glossary in patients that had more than six months of disease, medication currently in use (prednisone, hydroxychloroquine, immunomodulators including biologics: methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab), antiphospholipid syndrome (APS) according to 2006 revised Sapporo criteria [33], and evaluation of NPSLE applying the ACR Ad Hoc Committee on Neuropsychiatric Lupus nomenclature [34].
2. Neuropsychological evaluation was done by a psychologist: Hospital Anxiety and Depression Scale (HADS) [35] to assess self-reported symptoms of depression or anxiety, Mini International Neuropsychiatric Interview (MINI-Plus) [36] to assess major depression and suicidal risk according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) [37], and Cambridge Neuropsychological Test Automated Battery (CANTAB) [38] to assess cognitive deficit. Domains measured were attention (reaction time and rapid visual memory tests), visuospatial memory (paired associates learning tests) and executive functions (intra/extradimensional shift, stockings of Cambridge and spatial working memory tests). Cognitive deficit definition: score below $-2SD$ in at least

one outcome measure in two or three domains, following the ACR committee criteria [39].

3. Health-related quality of life: Medical Outcomes Study Short-Form 12 version 2 (SF-12v2) validated for SLE [40].
4. Autoantibodies: anti-double-stranded DNA (anti-dsDNA), anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-RNP, and antiphospholipid (APL) antibodies: anticardiolipin, anti-β2 glycoprotein I, and lupus anticoagulant tests were assessed. Anti-neuronal antibodies: anti-dsDNA/NMDAR by ELISA performed in Dr. Betty Diamond’s laboratory (Feinstein Institute for Medical Research, Manhasset, NY, USA) in 88 patients, and anti-P by commercial ELISA (IMMCO Co) confirmed by immunoblot of recombinant P0 protein in 93 patients. In 58 patients, anti-NSPA was detected by immunoblot implemented in our laboratory using 50 μg of mouse hippocampal extracts as the antigen. These anti-NSPA antibodies lacked

reactivity against the P0 protein and therefore recognize an epitope distinct from the P epitope in the NSPA protein. Each serum was diluted (1:100) and incubated for two h at room temperature. The blot was developed with alkaline phosphatase reaction and the bands were quantified with ImageJ software. Two units above the value of negative controls were considered positive. Each blot was repeated three times independently. As positive control, rabbit anti-NSPA protein was used as described [25].

Follow-up: SDI and SLEDAI-2K were obtained from records in 99 patients that had at least one follow-up visit.

Statistics

Data are presented in median and interquartile range (IQR: percentiles 25th–75th), mean (standard deviation), and

Table 1 Features of the cohort at entry according to presence of baseline damage and damage accrual in 99 female patients with SLE

N	Total	Baseline damage		p value	Accrual damage*		p value
		Without (SDI = 0)	With (SDI ≥ 1)		Without (baseline SDI + 0)	With (baseline SDI + 1 or more)	
99	99	60	39		88	11	
Age, years; median (IQR)	36.0 (27.0–45.0)	31.0 (25.0–40.8)	44.0 (35.0–54.0)	<i>< 0.001^A</i>	36.0 (27.3–44.8)	28.0 (24.0–45.0)	0.601 ^A
SLE duration, years; median (IQR)	3.7 (0.4–12.4)	1.5 (0.2–5.1)	12.0 (3.8–18.9)	<i>< 0.001^A</i>	3.7 (0.3–13.2)	2.5 (0.5–8.8)	0.502 ^A
Education, years; median (IQR)	14.0 (12.0–15.3)	14.0 (12.0–16.0)	13.0 (12.0–15.0)	0.165 ^A	14.0 (12–15.8)	13.5 (11.8–15.5)	0.646 ^A
Antiphospholipid syndrome (%)	9.2	1.7	20.5	0.002 ^B	8.0	18.2	0.266 ^B
SLEDAI-2K; median (IQR)	6.0 (3.0–12.0)	6.0 (4.0–12.0)	4.0 (2.0–12.0)	0.537 ^A	4.5 (2.0–11.5)	10.0 (6.0–22.0)	0.007 ^A
SDI score; median (IQR)	0 (0–1.0)	0 (0–0)	2.0 (1.0–2.0)	–	0 (0–1.0)	0 (0–4.0)	0.172 ^A
SDI ≥ 1 (%)	39.4	60.6	39.4	–	38.6	45.5	0.748 ^B
Corticosteroids use (%)	81.8	76.7	89.7	0.081 ^A	83.0	72.7	0.380 ^B
Hydroxychloroquine (%)	83.7	88.3	76.3	0.100 ^B	84.1	80.0	0.512 ^B
Immunomodulator use (%)**	46.9	43.3	52.6	0.245 ^B	42.0	90.0	0.004 ^B
Anti-dsDNA (%)	49.0	48.3	50.0	0.518 ^B	47.7	60.0	0.344 ^B
Anti-Ro (%)	41.4	38.3	46.2	0.286 ^B	40.9	45.5	0.508 ^B
Anti-La (%)	19.2	16.7	23.1	0.296 ^B	19.3	18.2	0.646 ^B
Anti-RNP (%)	36.4	36.7	35.9	0.556 ^B	36.4	36.4	0.638 ^B
Anti-Sm (%)	27.3	28.3	25.6	0.478 ^B	26.1	36.4	0.346 ^B
Anti-dsDNA/NMDAR (%)***	19.3	18.2	21.2	0.466 ^B	20.0	12.5	0.517 ^B
Anti-P (%)***	11.8	12.5	10.8	0.539 ^B	10.8	20.0	0.336 ^B
Anti-NSPA (%)***	5.2	8.1	0.0	0.252 ^B	2.0	25.0	0.047 ^B
Antiphospholipid antibodies (any); %	24.7	20.3	31.6	0.156 ^B	26.4	10.0	0.235 ^B

Data are in median and interquartile range (IQR: percentiles 25th–75th) or percentage: %. SDI SLICC/ACR Damage Index. *Accrual damage after a follow-up of median 55 (39–78) months: 54 (40–78) in group without new damage and 67 (22–87) in group with damage accrual, *p* = 0.363. **Immunomodulators include the following: methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, and 2 patients treated with rituximab. ***Anti-dsDNA/NMDAR was assessed in 88 patients, anti-ribosomal P (anti-P) in 93 patients, and anti-neuronal surface P antigen (anti-NSPA) antibodies in 58 patients. ^A Mann-Whitney *U* test; ^B Fisher’s exact test
Significant values (*p* < 0.05) are presented in italics.

frequencies in number (percentages). Patients were divided into two groups according to the presence or absence of baseline damage, and according to the accrual of new damage (SDI score change ≥ 1) or no change (SDI score change = 0) at the last follow-up visit. To evaluate the impact of variables on baseline damage and accrual damage, a univariate analysis was performed. Continuous variables were assessed with Mann-Whitney *U* test: age, disease duration, years of education, SLEDAI-2K score, SDI score, SF-12v2 physical and mental components, and HAD scores at baseline. Dichotomous variables were assessed with Fisher's exact test: APS, patients with SDI score ≥ 1 , corticosteroid use, hydroxychloroquine use, immunomodulator use including biologics, antibodies positivity (anti-dsDNA, Ro, La, RNP, Sm, anti-dsDNA/NMDAR, anti-P, anti-NSPA, any antiphospholipid antibodies), patients with major depression, suicidal risk, cognitive

deficit, attention domain $< -2SD$, spatial memory $< -2SD$, and executive functions domain $< -2SD$.

ANCOVA and regression analysis were performed for final SDI outcome and new damage accrual outcome, respectively. Baseline factors included were those with potential for influencing damage according to literature review and univariate results: age, education, disease duration, SLEDAI-2K, SDI, cognitive deficit, HAD depression score, presence of APS, prednisone use, immunomodulator use including biologics, anti-dsDNA positivity, anti-P, and anti-NSPA. Models were performed with and without anti-NSPA antibodies considering that this autoantibody was measured in 58 SLE patients. Significance level was set at 0.05 in all analyses performed.

Statistics were executed using SPSS version 17.0 (2008; SPSS Inc., Chicago, IL, USA).

Table 2 Distribution of organ damage according to SLICC/ACR Damage Index (SDI) at the end of follow-up

SDI domain	<i>N</i> (%) out of 99 SLE patients*	Organ damage item	<i>N</i> out of 39 patients with baseline damage (SDI ≥ 1)	<i>N</i> out of 11 patients with accrual damage (baseline SDI + 1 or more)
Neuropsychiatric	19 (19.2%)	Cerebrovascular accident	7	0
		Seizures for 6 months	5	1
		Cognitive impairment/major psychosis**	3	1
		Transverse myelitis	3	0
		Cranial or peripheral neuropathy	2	0
Musculoskeletal	16 (16.2%)	Avascular necrosis	6	2
		Osteoporosis with fracture	3	1
		Deforming or erosive arthritis	1	2
		Muscle atrophy or weakness	1	1
Ocular	9 (9.1%)	Retinal change/optic atrophy	8	1
Skin	6 (6.1%)	Scarring chronic alopecia	5	0
		Extensive scarring	4	0
Renal	6 (6.1%)	Glomerular filtration rate $< 50\%$	3	0
		Proteinuria > 3.5 g/24 h	3	0
Pulmonary	5 (5.1%)	Pulmonary hypertension	2	1
		Pulmonary fibrosis	1	0
		Shrinking lung	1	0
Peripheral vascular	5 (5.1%)	Venous thrombosis	3	2
Diabetes	4 (4.0%)	Diabetes	2	2
Premature gonadal failure	3 (3.0%)	Premature gonadal failure	2	1
Cardiovascular	2 (2.0%)	Myocardial infarction	1	0
		Valvular disease	1	0
		Pericarditis for 6 months	1	0
Malignancy	2 (2.0%)	Malignancy	1	1
Gastrointestinal	0 (0%)	Gastrointestinal	0	0

*At the end of follow-up, 45 (45.5%) patients had organ damage with SDI score ≥ 1 . Numbers do not add up because some patients had more than one item of damage. **Cognitive impairment assessed by medical evaluation in the SDI score and present at least six months

Results

Ninety-nine female SLE patients were included in this study. Baseline cohort features are presented in Table 1. In all, 22 (25%) out of 88 patients had anti-neuronal antibodies in different combinations: anti-dsDNA/NMDAR only in 13, anti-P/anti-dsDNA/NMDAR in four, and anti-P only in five. Interestingly, we found previously not described antibodies that recognize NSPA but that lack reactivity against the P epitope. These anti-NSPA antibodies were present in three out of 58 patients (5.2%).

Fifty-three (53.4%) patients presented at least one NPSLE syndrome at study entry (detailed information in Online Resource Supplementary Table 2). Major depression was present in 21.8%, cognitive deficit in 18.4%, together in 3.4%, and no depression nor cognitive deficit in 63.2%. After a median follow-up of 55 (interquartile range of 39–78) months, there were 11 (11.1%) patients who developed new damage, with a similar follow-up duration to the 88 patients without new damage. New damage appeared in musculoskeletal (five cases), neuropsychiatric (three cases), cardiovascular (two cases), ocular (one case), pulmonary (one case), peripheral vascular (one case), diabetes (two cases), and premature gonadal failure (one case) domains. Table 2 shows the total distribution of organ damage in different SDI domains in the 45 patients with SDI ≥ 1 at the end of follow-up. Most frequently affected domains were neuropsychiatric (19.2%), followed by musculoskeletal (16.2%) and ocular (9.1%). No patient died during the follow-up.

Risk factors for damage

Table 1 shows demographic- and disease-related factors according to the presence of damage score ≥ 1 at baseline and to accrual damage. Significantly associated with SDI ≥ 1 at entry were being older (median 44.0 versus 31.0 years, $p < 0.001$), having longer disease duration (median 12.0 versus 1.5 years, $p < 0.001$), and having APS (20.5% versus 1.7%, $p = 0.002$). The 11 patients that acquired new damage (baseline SDI score + 1 or more) had higher disease activity (median SLEDAI-2K score of 10.0 versus 4.5; $p = 0.007$), had been prescribed immunomodulators more frequently (90.0% versus 42.0%, p value = 0.004), and were anti-NSPA positive at a higher percentage (25.0% versus 2.0%; p value = 0.047).

Table 3 shows the evaluation of quality of life and neuropsychological assessment of the cohort at study entry. HRQoL physical component mean percentage (41.7%) and mental component mean percentage (36.2%) were similar between patients with or without accrual damage. The presence of cognitive deficit (19.0%), major depression (24.4%), and suicidal risk (23.8%) was also not associated with new damage.

In multivariate analysis, Table 4 shows ANCOVA for final damage score and Table 5 regression analysis for accrual damage in models with or without anti-NSPA antibodies. Final damage was significantly associated with SDI score, anti-NSPA positivity, and immunomodulators (including two patients treated with rituximab) ($p < 0.05$). In a model excluding anti-NSPA, SLEDAI-2K score emerged as another

Table 3 Quality of life and neuropsychological assessment of the cohort at study entry according to the presence of damage accrual

N	Accrual damage*		
	Without (baseline SDI + 0)	With (baseline SDI + 1 or more)	p value
88	88	11	–
Quality of life (SF-12v2)**			
Physical component; median (p25–75)	40.3 (33.9–49.7)	41.8 (26.7–51.5)	0.711 ^A
Mental component; median (p25–75)	34.9 (25.0–47.9)	43.8 (27.2–56.1)	0.243 ^A
Psychological assessment**			
Major depression (%)	24.4	11.1	0.334 ^B
Suicidal risk (%)	23.8	12.5	0.417 ^B
HAD depression score; median (p25–75)	5.0 (2.0–9.0)	4.5 (1.3–10.3)	0.837 ^A
HAD anxiety score; median (p25–75)	9.0 (5.0–13.0)	8.0 (4.5–11.5)	0.541 ^A
Neurocognitive assessment (CANTAB)**			
Cognitive deficit (< –2SD in 2 or more domains) (%)	19.0	12.5	0.546 ^B
Attention domain < –2SD (%)	17.7	12.5	0.583 ^B
Spatial memory domain < –2SD (%)	10.1	12.5	0.599 ^B
Executive functions domain < –2SD (%)	67.1	37.5	0.103 ^B

*After follow-up of median (p25–p75) 55 (39–78) months. **SF-12v2 (Study Short-Form 12) was assessed in 88 patients physical component and 87 patients mental component; major depression was assessed in 95 patients; HADS (Hospital Anxiety and Depression Scale) was assessed in 87 patients; suicidal risk was assessed in 88 patients; CANTAB (Cambridge Neuropsychological Test Automated Battery) was assessed in 87 patients. ^A Mann-Whitney U test; ^B Fisher’s exact test

Table 4 Analysis of covariance: baseline lupus factors influencing final damage in 99 lupus patients

	β coefficient	95% confidence limits	<i>p</i> value	R^2
Final SDI				0.819
Intercept	1.440	0.79–2.09	< 0.001	
SDI	1.058	0.92–1.20	< 0.001	
Anti-NSPA positivity	1.166	0.50–1.83	0.001	
Immunomodulator use (yes)	0.321	0.03–0.61	0.032	
Final SDI excluding anti-NSPA				0.887
Intercept	0.108	– 0.10–0.31	0.746	
SDI	1.099	1.02–1.18	< 0.001	
Immunomodulator use (yes)	0.269	0.07–0.47	0.008	
SLEDAI-2K	0.018	0–0.04	0.045	

Candidate variables considered were as follows: age, education, disease duration, SLEDAI-2K, SDI, cognitive deficit by Cambridge Neuropsychological Test Automated Battery (CANTAB), depression score of the Hospital Anxiety and Depression Scale (HAD), presence of antiphospholipid syndrome, prednisone use, immunomodulator use (including methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, and rituximab), anti-dsDNA positivity, anti-ribosomal P (anti-P), and anti-neuronal surface P antigen (anti-NSPA) antibodies positivity

influencing factor. Accrual damage was associated with anti-NSPA, and when this antibody was not considered, immunomodulator use and SLEDAI-2K score were predictors of new damage.

Anti-NSPA-positive patients had severe lupus onset previous to their participation in this study: two patients had lupus nephritis (LN) and another had lupus encephalopathy, requiring therapy with high doses of corticosteroids. None of them had baseline damage, but two had added damage during follow-up attributed to high doses of corticosteroid use: avascular necrosis of bone and diabetes.

Table 5 Regression analysis: baseline lupus factors influencing damage accrual in 99 lupus patients

	OR	95% confidence limits	<i>p</i> value
New damage accrual			
Intercept	0.085	–	0.024
Immunomodulator use (yes)	12.64	0.88–182.47	0.062
SLEDAI-2K	1.130	0.996–1.28	0.057
Anti-NSPA positivity	17.604	1.13–273.52	0.040
New damage accrual excluding anti-NSPA			
Intercept	0.20	–	< 0.001
Immunomodulator use (yes)	11.866	1.39–101.53	0.024
SLEDAI-2K	1.149	1.03–1.29	0.016

Candidate variables considered were as follows: age, education, disease duration, SLEDAI-2K, SDI, cognitive deficit bay Cambridge Neuropsychological Test Automated Battery (CANTAB), depression score of the Hospital Anxiety and Depression Scale (HAD), presence of antiphospholipid syndrome, prednisone use, immunomodulator use (including methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, and rituximab), anti-dsDNA positivity, anti-ribosomal P (anti-P), and anti-neuronal surface P antigen (anti-NSPA) antibodies positivity

Discussion

Damage predicts future mortality in lupus [2]. Therefore, it is important to understand which factors are related to their damage development to implement measures that could improve life expectancy with less morbidity in SLE patients. In this 99 SLE patient cohort, clinical factors including cognitive function and anti-neuronal antibodies that may influence damage at five-year follow-up were studied.

Our results showed presence of damage in 45.5% of patients at the last follow-up. This is in the lower damage range (50–80%) of published studies with similar disease duration. Damage accrual was observed in 11.1% of patients. SDI score increased by mean 0.2 points which is also a low progression in comparison with the Hopkins Lupus Cohort (0.1 points per year) [41], and with the 17 studies reviewed by Sutton et al. that assessed damage at two time points (0.3–1.8 point of the SDI score) [2]. The exclusion of male and hospitalized patients may explain the low damage accumulation in our cohort. In agreement with several studies, older age, longer disease duration, and APS were associated with baseline damage [2].

Active lupus patients were included, as median SLEDAI-2K score was 6.0, and our findings concur with the proposed role of higher disease activity in damage accrual [42]. In addition, independent of SLEDAI-2K score in multivariate analysis, immunomodulator use paradoxically associates with accrual damage [3, 43]. This may be due to more severe disease requiring cytotoxics or biologics and adverse effects of these drugs reflected in the index.

Even though antimalarial use has a described protective role in damage accumulation [9, 10], we did not find this effect, likely as most patients were on antimalarials at baseline. Hydroxychloroquine was suspended in eight patients due to retinopathy development. The

impact of APS on baseline damage was not reproduced in damage accrual. This might be due to the anticoagulant therapy. Interestingly, SDI score at baseline was associated with final damage but was not a predictor of new damage, in contrast with other cohorts [2, 42].

The contribution of cognitive impairment to organ damage has been analyzed in previous studies but the data is not conclusive. Tomietto et al. [14] report an association of SDI with the number of cognitive-impaired functions, while Petri et al. [15] describe higher SDI in patients with poorer performances in spatial recognition and continuous performance tests. In addition, Conti and collaborators [16, 17] describe global cognitive dysfunction correlated with damage index at entry and at follow-up. The comprehensive neuropsychological assessment applied at baseline in our previous work [19] allowed us to investigate the association of cognitive deficit with damage at follow-up. In contrast with other studies, neither cognitive deficit nor any particular domain function impairment affected damage in our cohort. Dissimilar cognitive tests applied and definition criteria of cognitive impairment may explain these different findings. As cognitive function might change, and even improve over time [17], it is difficult to ascribe a detrimental effect to this condition.

Our results agree with previous studies [6, 9, 44] indicating that depression and HRQoL scores do not associate with accrual damage. Neither was suicidal risk associated with damage in our cohort. We have reported evidence that depression associates with lower HRQoL [28] but not with cognitive deficit [18].

In summary, our longitudinal cohort design provides an analysis of damage accrual and influencing factors. In-depth evaluation of neuropsychiatric variables and anti-neuronal antibodies permitted to properly address the impact of cognitive deficit, depression, HRQoL, and anti-neuronal antibodies on damage. Also, multivariate analysis clears the influence of each variable on the outcomes. To our knowledge, this is the first study assessing the role of anti-neuronal antibodies in lupus damage in the follow-up. Anti-P and anti-dsDNA/NMDAR were not related to damage, while anti-NSPA antibodies emerged as a potential factor of worse outcome. Two patients with anti-NSPA positivity presented new damage (avascular necrosis of bone in the case with LN and diabetes in the case with lupus encephalopathy), probably related to the use of high corticosteroid doses indicated for their severe lupus onset. We are aware of the limited number of anti-NSPA-positive patients (5%). Also, we acknowledge that the follow-up period of 55 (IQR of 39–78) months is relatively short. Further studies with larger numbers of patients are needed to confirm this association and whether induced damage is related to lupus disease or drug adverse effects. There are other limitations in this study. Our results only apply to female SLE patients. Separation by gender in SLE in clinical research might better identify factors contributing to severity [28]. In addition, our study was not an inception cohort. Patients had a

median of 3.7 years of lupus (interquartile range of 0.4–12.4) and 39% had damage at cohort entry; therefore, information regarding damage accumulation in the first years was lost.

The most important predictors of damage appeared to be immunomodulator use and disease activity. This implies that better treatment is an unmet need in SLE. The potential influence of anti-NSPA antibodies on damage accrual raises the possibility that anti-neuronal antibodies might play a role on outcome.

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Data availability The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Disclosures None.

Ethical statement All participants voluntarily signed an informed consent approved by the Pontificia Universidad Católica de Chile Ethical Committee prior to their inclusion in the study, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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