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ORIGINAL ARTICLE

Autoantibodies, elevated cytokines, and neurocognitive abnormalities in offspring of women with systemic lupus erythematosus: comparison with healthy controls

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Abstract

Introduction Research describes higher incidence of neurodevelopmental disorders and learning disabilities in offspring of women affected by lupus. Factors implied are pregnancy and delivery adversities and exposure to maternal antibodies and cytokines. Little is known about the offspring immunological condition or the relation between offspring and maternal condition.

Objectives This study was conducted in order to analyze immunological configuration, psychopathology, and neuropsychological performance of young offspring of women with lupus, in comparison with healthy controls and in relation to maternal psychophysical condition.

Methods Twenty-one offspring aged 8–17 of 17 women with lupus and 34 controls were recruited. Pregnancy conditions, stress factors, and immunological, psychopathological, and neuropsychological characteristics were compared. Immunological tests included standard lupus screening, lupus-related autoantibodies, antibodies against GluN2 subunit of the *N*-methyl-D-aspartate receptor (NMDAR) (anti-DWEYS Ab), and levels of ten cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, GMCSF, IFN-γ, TNF-α).

Results Offspring had lower leukocyte count ($p = 0.001$) and higher levels of anti-dsDNA Ab ($p = 0.022$), anti-DWEYS-GluN2 Ab ($p < 0.001$), and eight cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, TNF-α—all $p < 0.001$—and IFN-γ, $p = 0.026$) than

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controls. Their cytokine levels did not differ from their mothers'; 23.9% of offspring met the criteria for a clinical psychiatric diagnosis. No differences were found in intelligence measures. Various neuropsychological scores correlated inversely with maternal psychophysical health.

Conclusions Offspring's profile suggests proinflammatory and autoimmune activation. Their rate of psychiatric diagnosis appears higher than in the general population, and their cognitive performance is related to maternal psychophysical health. Longitudinal research might investigate whether immunological and psychosocial conditions influence psychopathology and cognition.

Keywords Anti-DWEYS · Anti-NMDA/glutamate receptor antibodies · Cognitive development · Cytokines · Parental depression · Systemic lupus erythematosus

Introduction

Increasing evidence suggests that the immune system can influence psychopathology and neurodevelopment and be affected by psychosocial stress. Children of mothers affected by systemic lupus erythematosus (SLE) represent an interesting and complex model in this respect. Studies suggest an increased risk of neurodevelopmental disorders such as autism spectrum disorders (ASD) and attention deficit and hyperactivity disorder (ADHD) in these offspring, as well as higher frequency of learning disabilities (LD) (reviewed in [1]). In addition to unspecific risk factors such as prematurity, low birth weight, and medication exposure, maternal IgG antibodies and cytokines would cross the placenta through an immature blood–brain barrier (BBB) and reach the fetal brain, altering neurodevelopment [1].

Research has, e.g., identified a subset of the anti-dsDNA antibodies, the anti-DWEYS-GluN2 Ab: in murine models, they cross the placenta and induce neuronal apoptosis in fetal brain by binding the *N*-methyl-D-aspartate receptor (NMDAR), causing cognitive impairment in offspring [2]. They react against the GluN2A/B subunit of the NMDAR and can be identified as binding the DWEYS peptide sequence in the receptor [3]. Another discussed mediator is IL-6. It is known for its primordial role in brain development [4] and can be elevated in SLE patients, where it is involved in autoantibody production. During SLE pregnancies, IL-6 could directly alter the development of the fetal brain [4] or indirectly enhance the production of maternal antibodies (reviewed in [1]).

These mediators act also on the SLE patients' brains [5], and they are considered responsible for the cognitive dysfunction, mood and anxiety disorders, psychosis, acute confusion state, and headache [6] seen in neuropsychiatric lupus (NPSLE).

Some works suggest that SLE offspring (SLE-O) have an increased risk for allergic and nonrheumatic autoimmune disorders [7, 8]. It is then arguable whether the immune mediators implied in NPSLE and in fetal damage are also produced independently in SLE-O during their growing up, and thus may trigger similar damage [9].

It is likewise arguable whether having a chronically ill parent throughout growing up can have an impact on SLE-O's psychophysical condition. Despite some sparse results [10–12], extensive studies on the immunity and inflammatory profile of SLE offspring have not been carried out yet.

Aims of the study

This study was conducted in order to investigate the immunological profile in a sample of young SLE-O, to compare them to a control sample of healthy subjects born to mothers without autoimmune disease, and to analyze SLE-O's neurocognitive function, comparing it to that of the controls.

A secondary objective was to explore possible associations between immunological/neurocognitive markers in SLE-O and maternal psychophysical condition.

Method

Subjects

All mothers followed up at the Outpatient Unit of the Department of Autoimmune Diseases, Hospital Clinic, Barcelona, with children aged 8–17, were invited to participate in the study together with their children, in the period June 2010–February 2012. Controls were community healthy children (HC) within the same age range as SLE-O, who did not meet any criterion for a psychiatric diagnosis and whose mothers whose mothers did not have a systemic rheumatic disorder. These criteria were chosen to confine possible effects of personal/familiar autoimmunity and of psychopathology within the offspring group. HC were recruited from local pediatric and family medicine practices within the Hospital Clínic's referral area and through local advertisement. Exclusion criteria for

HC included an acute or chronic medical condition, as well as regular medication intake, counting anti-inflammatory drugs. This cross-sectional study was approved by the Ethics Committee of Hospital Clínic, parents or legal guardians gave written informed consent before the study began, and subjects over 14 years old gave their assent. For each young subject, at least one parent was always also interviewed.

Measurement

Young subjects

Conditions of child pregnancy and delivery measured by the OCS (obstetrical complication scale [13]); birth weight and birth week; personal and family history of immune/allergic conditions (as in [14]); demographic measures such as age, gender, body mass index (BMI), and socioeconomic status (SES scale, as in [15]); data on family structure (intact vs reorganized family structure since child's conception, as in [15]); and family history of psychiatric diagnosis, were collected for the HC and SLE-O at the time of recruitment by interviewing the parents.

Immunological screening included the standard blood battery used at our hospital for the follow-up of SLE: leukocyte count and formula, C-reactive protein (CRP), complement (C3, C4, CH50), and anti-double strand DNA [anti-dsDNA] and anti-nuclear [ANA], anti-Ro, anti-La, and anti-ribosomal antibodies.

Antibodies and cytokines associated in the literature with psychopathology and/or cognitive dysfunctions were also assessed: anti-thyroidal and anti-streptolysin-O (ASLO) antibodies, described in mood and obsessive–compulsive disorder (OCD)/tic/Tourette disorders, respectively [16, 17], and anti-DWEYS-GluN2 Ab determined by ELISA following the procedure described in [3], kindly provided by Dr. Diamond's Laboratory. Serum levels of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, GM-CSF, IFN-γ, and TNF-α were assessed by a Luminex ultra-sensitive kit, Invitrogen LHC6004, sensibility < 1 pg/mL, as described in [15]. All samples were assayed in duplicate and compared to a standard curve. Values below the detection threshold were set to zero, and extrapolated values were accepted as valid. Blood samples were collected with fasting, early morning extraction. Analyses were performed at the Core Facility and Immunology Department Laboratories of Hospital Clínic and used standard techniques unless elsewise indicated. Serum for specific tests was obtained by centrifugation at 2000 rpm for 10 min and then kept frozen at − 80°°C until the time of the assay (between 12 and 30 months after extraction).

Psychopathological screening was performed through the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL [18]), administered to young subjects and caregivers by a trained psychiatrist or psychologist. Psychiatric diagnosis was given according to DSM-IV criteria. Continuous measures of depression and anxiety were obtained using the Children's Depression Inventory (CDI, children under 16 years old) [19], the Beck Depression Inventory (BDI, children over 16 years old) [20], and the Screen for Child Anxiety Related Emotional Disorders (SCARED) [21]. Recent stress levels in subjects were assessed through the Stressful Life Events Schedule (SLES), child (SLES-C) and parent (SLES-P) versions [22].

The cognitive included the following: (1) *Wechsler intelligence scales* for children 4th edition (WISC-IV) and *Wechsler adult intelligence scale 3rd edition* (WAIS-III) for participants aged 7–16 and 17, respectively [23]; (2) *Rey–Osterrieth complex figure* test (ROCF) for perceptive abilities to organize a complex visual stimulus, visual–motor skills to copy it, and immediate visual memory [24]; (3) *Test of memory and learning* (TOMAL) for verbal and nonverbal attention processes and memory [25]; (4) *Tower of London* for planning abilities and executive functions [26]; (5) *Conners' Continuous Performance Test-Second Edition* (CPT-II) for attentional function [27]; and (6) *Reading (PROLEC) and Writing (PROESC) Process Assessment* for reading and writing learning abilities [28]. Results are presented in typical scores, with a mean of 50 and standard deviation of 10. Scoring 1.5 standard deviations below the mean suggests difficulties in the area.

Mothers

Disease activity in SLE mothers was assessed through the SLEDAI (SLE Disease Activity Index), measured both at recruitment point and retrospectively during pregnancy. Pregnancy value was calculated considering all the problems which occurred and remembered during that period; therefore, it can be considered an estimation of the highest SLEDAI reached during the whole pregnancy. Maternal physical condition and cumulative damage of disease were measured by the SLICC/ACR (Systemic Lupus International Collaborative Clinics/American College of Rheumatology) Damage Index (SLICC-DI) [29].

Mothers underwent the same immunological tests as young subjects.

Their psychopathological condition was assessed through the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and quantitatively by HADS (Hospitalary Anxiety and Depression) Scales [30]). Scores for HADS anxiety and depression subscales range from 0 to 21: not clinical 0–7, mild 8–10, moderate 11–14, and severe symptoms 15–21.

Statistical analysis

Continuous variables were described as median and interquartile range and compared by Mann–Whitney test. Categorical

variables were described as frequencies and percentages and compared between SLE-O and HC using Fisher exact test. Correlations between chosen continuous variables were assessed using Spearman's correlation. Univariate logistic regression was conducted on a set of variables, selected between those significantly different between SLE-O and HC at a $p < 0.05$ using clinical criteria. A multivariate logistic regression analysis was performed to search for markers characterizing the SLE-O condition, considering variables with a p value < 0.1 in the univariate testing.

Analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) or Statistical Package for Social Sciences version 20.0 (SPSS, Chicago, IL), and a level of significance was established at the two-sided 5% level.

Results

Sample description

Young subjects

Twenty-one offspring (SLE-O, $n = 21$, mean age 14.9, %female 40%) of 17 mothers and 34 healthy controls (HC, $n = 34$, mean age 15.1, %female 48%) were recruited. No significant difference was found in age, sex, BMI, and socioeconomic status, nor in maternal age at birth, between the two groups. SLE-O had significantly higher proportion of intact family structure (meaning biological parents still together) than HC (90.5 vs 66.7%, $p = 0.046$). No significant differences were found in the rates of psychiatric diagnosis in family members among the two groups (a maternal lifetime psychiatric diagnosis was present in 34% of HC and in 57.1% of SLE-O, $p = 0.102$). All HC and SLE-O had been conceived by natural fecundation. No significant difference was found in the rate of twin–triplet pregnancies or rate of siblings in the study. Offspring were more frequently only children (57.1 vs 9.9%, $p < 0.001$) and first children (76.2 vs 48.5%, $p = 0.043$).

SLE-O had more complications during pregnancy/delivery (OCS, median (IQR) for HC—.5 (1–3), and for SLE-O—4 (2–7), $p = 0.006$), and shorter pregnancy length than HC (week of delivery: HC—40 (39–40); SLE-O—38 (34–40), $p = 0.004$).

No significant difference was found in birth weight among the two groups ($p = 0.294$).

SLE mothers: physical health and psychopathological measures

Median for the disease activity scale SLEDAI in SLE mothers was 2 (IQR 0–6) during pregnancy and 3 at test point (0–10). At pregnancy, most patients (40%) had elevated anti-dsDNA Ab. Proteinuria, pericarditis, fever, arthritis, cytopenia, or mouth ulcers were described in single cases. At test point, the most frequent complaints were anti-dsDNA Ab (45%), reduction of complement and mouth ulcers (both 30%), and arthritis and pericarditis (15%), followed by cytopenia, proteinuria, and alopecia.

The median for the SLICC index at test point was 2 (1–5), mainly consisting of cognitive impairment and muscular weakness (38%). Myocardial infarction, malignancy, scarring alopecia, and erosive arthritis were present in single cases.

Disease scales correlated positively between each other (SLEDAI-current vs SLEDAI-pregnancy: $R = 0.708$, $p < 0.0005$; SLEDAI-current vs SLICC: $R = 0.543$, $p = 0.003$; SLEDAI-pregnancy vs SLICC: $R = 0.617$, $p = 0.001$). A lifetime psychiatric diagnosis was found in 53% of SLE women ($n = 9/17$): depression in 24% and anxiety, adjustment disorders, and affective disorder secondary to medical illness in 12% each. At test point, 30% of women met the criteria for a clinical psychiatric diagnosis (depression $n = 2$, anxiety $n = 2$, and affective disorder secondary to medical illness $n = 1$), and 35% more for a subclinical affective diagnosis. Median for the HADS-anxiety scale was 8 (7–11) and for the HADS-depression scale 6 (3–7). The two scales did not correlate significantly with each other. The HADS-depression scale—but not the anxiety scale—correlated with disease scales: SLEDAI-pregnancy (Spearman's $R = 0.756$, $p = 0.002$), SLEDAI-current ($R = 0.650$, $p = 0.009$), and SLICC ($R = 0.695$, $p = 0.004$).

Immunological results: comparisons of SLE-O versus HC

SLE-O had significantly higher proportions than HC of history of nonallergic autoimmune conditions (19 vs 0%, $p = 0.009$, one each: autoimmune glomerulonephritis, thyroid dysfunction, vitiligo, and cryoglobulinemia). There was no difference among overall allergic conditions between the two groups (32 vs 16%, $p = 0.20$); however, asthma was more frequent in SLE-O than in HC (24 vs 3%, $p = 0.018$). SLE-O had lower leukocyte, monocyte, and lymphocyte count than HC, albeit generally within normal range. Anti-dsDNA antibodies were quantitatively higher in SLE-O ($p = 0.022$), even though all subjects fell within the normal range. Anti-DWEYS-GluN2 Ab and eight cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IFN-γ, and TNF-α) were higher in SLE-O than in HC. Anti-Ro/SSA and anti-La/SSB Ab were negative in all young subjects. No other immunological differences were found between the two groups. See Table 1 for the results of continuous variables.

CRP showed a positive correlation with age in the SLE-O group but not in the controls ($R = 0.615$, $p = 0.025$ in SLE-O), and lymphocyte count had a negative correlation with age in the SLE-O ($R = -0.709$, $p = 0.001$) and not in the HC ($R = -$

0.330, $p = 0.057$). No association with age of subjects was found for the cytokines or autoantibodies in either group.

Neurocognitive testing: comparison between SLE-O and HC

No differences were found in IQ measures between the two groups, and almost all scores fell within the normal range (5% of SLE-O scored below 1.5 standard deviation below the intellectual cognitive index mean). SLE-O scored significantly differently from the HC in the three neuropsychological measures: time of copy in visual–spatial organization of Rey figure—SLE-O slower than HC (typical score = T.S. median [IQR] 45 (36–58) vs 59 (51–61), $p = 0.001$**); Tower of London, transgression of rules—SLE-O better performance, i.e., less transgressions, than HC (T.S. = 52 (52–53.5) vs 52 (35–52), $p = 0.002$**); and PROESC quality of writing—worse performance of SLE-O (T.S. = 47 (43–55) vs. 55 (45–65), $p = 0.039$*). Even though there were no significant differences between groups in the other learning assessments, a range of 10–20% of young subjects of the whole sample showed deficits in mechanical reading, 20–25% in reading comprehension, and 15–20% in words writing.

The working memory index of Wechsler scales, as well as the scores in verbal memory task and visual–spatial skills, showed a negative correlation with age in SLE-O, indicating that older children in SLE-O performed worse than younger

Table 1 Immunological data and comparisons between lupus offspring, healthy controls, and lupus mothers

	SLE-O $n = 21$	HC $n = 34$	SLE-M $n = 17$
*Leukocytes (RI 4–10*10^9/L)*[1]	*5.64 (4.84–6.51)*	*7.25 (6.45–8.74)*	5.57 (3.9–8.34)
*Neutrophiles (RI 2.5–7 *10^9/L)*[1]	*2.9 (2.4–3.5)*	*3.75 (3–5)*	3.35 (2.45–6.2)
*Lymphocytes (RI 0.9–4.5*10^9/L)*[2] *[M-O1; M-C1]*	*1.9 (1.6–2.5)*	*2.4 (1.9–2.9)*	1.35 (1.05–1.75)
PCRnum (RI < 1.00) [M-O4, M-C3]	*0.02 (0.02–0.04)*	*0.03 (0.02–0.04)*	0.07 (0.03–0.48)
C3 (RI 0.82–1.87 g/L) [M-O1, M-C1]	1.16 (1–1.23)	1.06 (0.96–1.14)	0.92 (0.87–1.03)
C4 (RI 0.11–0.45 g/L)	0.23 (0.2–0.29)	0.26 (0.2–0.29)	0.19 (0.13–0.27)
CH50 (RI 34–71 U/mL)	44 (28–53)	45 (38–50)	46 (31.5–50.5)
Anti-dsDNA (RI < 10 UI/mL)[4] *[M-O3, M-C3]*	*1.3 (0.65–3.25)*	*0.7 (0.3–1.1)*	18 (2.2–45)
ANA (RI <= 3 +) [M-O4, M-C3]	3 (2–4)	3 (2–4)	6 (5–8)
Anti-ribosomal Ab (RI < 12 UI/mL)	1.6 (1–3)	1 (1–13)	2 (1–2.9)
Anti-DWEYS-GluN2 Ab (UI/ml) [3] *[M-O2, M-C3]*	*0.15 (0.12–0.2)*	*0.07 (0.05–0.1)*	0.1 (0.07–0.14)
ASLO Ab (RI < 200 UI/mL) [M-O1, M-C1]	232 (122–346)	300.5 (155–523)	104 (28–159)
Anti-TPO Ab (RI < 35 UI/mL)	40 (37–48)	48.5 (39–57)	41 (34–50)
Anti-TG-Ab (RI < 60 UI/mL)	27 (23–30)	31 (25–36)	28 (21–36)
IL-1β (pg/ml) [3] *[M-C3]*	*0.71 (0.39–0.94)*	*0 (0–0)*	0.72 (0.55–0.86)
IL-2 (pg/ml) [3] *[M-C3]*	*0.39 (0.13–3.24)*	*0 (0–0)*	0.42 (0–10.65)
IL-4 (pg/ml) [3] *[M-C3]*	*2.52 (1.51–6.65)*	*0 (0–0)*	4.01 (0–24.87)
IL-5 (pg/ml) [3] *[M-C3]*	*0 (0–0.31)*	*0 (0–0)*	0 (0–0.71)
IL-6 (pg/ml) [3] *[M-C3]*	*0.82 (0.46–1.81)*	*0 (0–0.38)*	1.82 (1.01–4.47)
IL-8 (pg/ml)	16.66 (9.99–24.82)	12.43 (9.77–16.49)	13.26 (11.58–16.95)
IL-10 (pg/ml) [3] *[M-C3]*	*0.56 (0.12–1.02)*	*0 (0–0)*	0.38 (0.24–1.56)
IFN-γ (pg/ml) [4]	*0.2 (0–1.07)*	*0 (0–0)*	0 (0–1.07)
TNF-α (pg/ml) [3] *[M-C3]*	*0.58 (0.23–1.73)*	*0 (0–0)*	0.41 (0.23–7.7)
GMCSF (pg/ml)	0 (0–0)	0 (0–3.08)	0 (0–0)

In italics, the parameters significantly different between offspring and controls. Descriptive statistics are median [interquartile range]

SLE-O = offspring of women with lupus; *HC* = healthy controls; *SLE-M* = women with lupus; *Anti-dsDNA Ab* = antibodies against double-stranded DNA; *ANA* = anti-nuclear antibodies; *ASLO Ab* = anti-streptolysin-O Ab; *Anti-TPO Ab* = anti-thyroid peroxidase Ab; *Anti-TG Ab* = anti-thyroglobulin Ab; *Anti-DWEYS-GluN2 Ab* = Ab against the DWEYS peptide of the GluN2 subunit of the NMDAR identified in SLE patients [2] and determined by ELISA; RI = laboratory reference interval; *M-O1* = SLE-M<SLE-O, $p < 0.01$**; *M-O2* = SLE-M<SLE-O, $p < 0.05$*; *M-O3* = SLE-M>SLE-O, $p < 0.01$**; *M-O4* = SLE-M>SLE-O, $p < 0.05$; *M-C1* = SLE-M<HC, $p < 0.01$**; *M-C3* = SLE-M>HC, $p < 0.01$**

[1] SLE-O<HC, $p < 0.01$**

[2] SLE-O<HC, $p < 0.05$*

[3] SLE-O>HC, $p < 0.01$**

[4] SLE-O>HC, $p < 0.05$*

ones in selective attention and immediate memory and in drawing. No relations between other neuropsychological scores and age were found in the HC group (Table 2).

Psychopathological testing in SLE-O

A fraction of SLE-O (23.9%) was found to meet the criteria for a clinical psychiatric diagnosis, corresponding to a confidence interval (CI) for the estimated prevalence of clinical psychiatric diagnosis in the SLE-O population of [10.6–45.1%]. Diagnoses were ADHD ($N = 2$, frequency = 10%), anxiety, Tourette syndrome, and OCD (all $n = 1$, 5%). Another half of SLE-O ($n = 9$, 52%) had a subclinical diagnosis of the following: anxiety (9; 43%), ADHD (4; 19%), and OCD (1; 5%).

Controls were psychopathologically healthy by recruitment criteria, thus not comparable. In the young population from the same geographical area (GYP) as our subjects, the estimated prevalence for any axis I diagnosis is between 9.5 and 13% [31]. The resulting likelihood that the prevalence of clinical psychiatric diagnosis in SLE-O is not different from that in the general youth population ranged between 2–14 and 2%.

SCARED median score was 13 (IQR = 9–19) in HC and 19 (13–24) in SLE-O, BDI depression scale was 2 (0–5) in HC and 5 (1–8) in SLE-O, and SLE score was 14 (6–17) in HC and 20 (10–42) in SLE-O. No significant correlation was found between age and psychopathological or stress scales in either group.

Multiple regression analysis within SLE-O and HC

To look for parameters defining the SLE-O condition, in comparison with that of HC, multiple logistic regression analysis was performed with a forward stepwise adjustment. Independent variables were chosen to represent the different data sets (personal history of autoimmune disease, pregnancy conditions, white cells, cytokines, antibodies, neurocognitive performance) among those significantly different between the two groups at $p < 0.05$. The regression analysis selected anti-DWEYS-GluN2 Ab as the most significant variable ($p = 0.012$, OR [95% CI] 38.38 [2.25–654.44]), together with leukocyte count ($p = 0.059$, OR = 0.28 [0.08–1.05] and text writing abilities ($p = 0.051$; OR = 0.77 [0.59–1.00]) (Table 3).

Secondary results: comparison with mothers' immune profile and correlations between offspring and mothers' parameters

Both SLE-O and HC had higher lymphocyte and eosinophil counts than the SLE mothers and lower CRP, higher C3 fraction of complement, lower anti-dsDNA and anti-nuclear Ab, and higher ASLO antibodies than the SLE mother group. Anti-DWEYS-GluN2 Ab in mothers were higher than in HC and lower than in SLE-O. Mothers' cytokine levels were not different from SLE-O, and their IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, and TNF-α levels higher than in HC (Table 1 and Fig. 1).

Correlations between maternal conditions and neurocognitive, anxiety, and depression scores in their children showed that maternal disease and depression (but not anxiety) scales correlated positively with children's depression (but not anxiety) and stress scales and negatively with various neuropsychological performance indexes. The correlations were higher and more frequent with maternal disease activity scale measured at test point, than during pregnancy (Table 4).

Discussion

This is an exploratory study on offspring of SLE mothers. Offspring show an immune profile that is different from that of relevant HC, with lower leukocyte counts and higher levels of mainly proinflammatory cytokines and of anti-dsDNA Ab. An antibody that has been described as possibly neurotoxic and related to psychiatric symptoms in SLE patients, the anti-DWEYS-GluN2 Ab, is significantly higher in SLE-O, and its

Table 2 Relation between neuropsychological tests and age between lupus offspring and healthy controls

Neuropsychological parameters	SLE-O Spearman's rho (p value)	HC
Wechsler—Working Memory Index	− 0.640** (0.002)	0.002 (0.992)
TOMAL Test—Verbal memory–curve	− 0.495* (0.023)	0.14 (0.429)
ROCF—quality of copy	− 0.555** (0.009)	0.087 (0.631)

Wechsler—Working Memory Index = Working Memory Index from Wechsler intelligence scales; *TOMAL Test—verbal memory–curve* = test of memory and learning, subtest of verbal memory, learning curve; *ROCF—quality of copy* = Rey–Osterrieth complex figure test, measure for visual memory and drawing skills; *SLE-O* = offspring of women with Lupus; *HC* = healthy controls

Table 3 Uni- and multivariate logistic regression analysis, for lupus offspring condition

	Univariate model	Multivariate model		
	p value	OR [95% CI]	*p* value	OR [95% CI]
History of autoimmune or allergic disease	0.029	4.20 [1.16–15.19]		
OCS	0.004	1.54 [1.15–2.06]		
Leukocytes total count	0.004	0.49 [0.31–0.79]	0.059	0.28 [0.08–1.05]
IL-6	0.047	1.83 [1.01–3.34]		
Anti-DWEYS-GluN2 Ab	0.000	7.56 [2.51–22.79]	0.012	38.38 [2.25–654.44]
PROESC—quality of writing	0.066	0.95 [0.91–1.00]	0.051	0.77 [0.59–1.00]

Multivariate model was constructed using a forward stepwise with above indicated variables (all had a $p < 0.1$ on the univariate testing). ROC AUC, 0.947 [0.882–1.00]

SLE-O = offspring of women with lupus; *OCS* = Obstetrical Complication Scale; *IL-6* = interleukin-6; *Anti-DWEYS-GluN2 Ab* = antibodies against the GluN2A/B subunit of the *N*-methyl-D-aspartate receptor; *PROESC* = learning abilities text-writing

levels can define this group with high odds ratio, making it a possible biomarker for the offspring condition.

Neuropsychological tests show no differences in intelligence parameters in comparison with healthy controls. However, the significantly different performance of SLE-O in some subtests reflects more difficulties in written production, greater slowness in visual–motor abilities, and better impulsivity control in comparison with healthy controls. Furthermore, older SLE-O perform worse than those younger in attention and immediate memory, suggesting a possible worsening over time.

SLE-O show also a rate of psychiatric diagnosis seemingly higher than that of the general population, especially at the expense of attention deficit and anxiety disorders, consistent with previous studies [1].

Parallelly, current maternal psychophysical condition seems linked to both offspring's mood and neurocognitive performance, also in line with other studies.

The immunological findings might just be the indication of a familiar subclinical autoimmunity: little is known about cytokine profiles in SLE relatives, but higher anti-DWEYS-GluN2 Ab [10] and anti-nuclear Ab [32] have been reported in first-degree relatives of SLE patients, and a familial aspecific dysfunction of the B lymphocyte has been posited. Whether these are responsible factors in the higher prevalence of autoimmune and allergic disease found in SLE offspring [7, 8], or just casual findings, is not known yet.

Speculatively, cytokines and anti-DWEYS-GluN2 Ab might represent an inflammatory milieu, that for a long time could progressively affect these subjects both systemically and centrally, as described in the course of SLE disease.

Cytokines in SLE are involved in cardiopulmonary, cutaneous, and renal affection, by acting both on immune cells and on local cells, as the endothelial cells [33]. Increased circulating IL-6 seems characteristic of an inflammatory neurological condition, and CSF levels of IL-6, IL-8, and IL-10 have shown to correlate with NPLSE disease activity (reviewed in [34]). In particular, IL-10, predominantly an anti-inflammatory cytokine, may acquire proinflammatory activity during immune responses and a pathogenic role in SLE [35, 36].

Parallel research from child and adolescent psychiatry has associated systemic proinflammatory condition and elevated cytokines, with inflammatory and immunological processes in the brain, resulting in insults to brain parenchyma and progressive development of psychopathology along the lifespan [37–40].

Anti-DWEYS-GluN2A Ab have been associated with damage of non-nervous tissue, such as bone, pancreas, and skin [41], but also blood cells, relating with reduced counts of leukocytes [42]. In murine models, they can cause cognitive impairment (especially hippocampus-dependent memory impairment) [43]. Human studies have often found an association between intrathecal anti-DWEYS-GluN2 Ab levels and NPSLE manifestations (reviewed in [44]) and sometimes between serum anti-DWEYS-GluN2 Ab and cognitive dysfunction or decline in cognitive performance over time [45] in both adult and pediatric SLE patients, as well as depressive mood in adult patients. Inconsistencies in results might be related to the need of a breach in the BBB for the antibodies to reach the CNS, both in animal and human studies (reviewed in [6, 44]).

The same processes might occur also in SLE offspring, where it would be only with repetitive passages through the BBB that these mediators could affect development and cause some of the same alterations described in SLE women.

The findings that older SLE-O had lower leukocyte count and higher CRP and performed worse in attention and immediate memory than younger ones are compatible with this hypothesis of a progressive action.

Anti-DWEYS-GluN2 Ab in SLE-O were also higher than in SLE mothers. This is an interesting datum. Longitudinal explorations might clarify whether there is a trend along the lifespan in this parameter, where the titers tend to go down with age in SLE patients and relatives. If so, the antibodies may be the expression of nonspecific autoimmunity, possibly

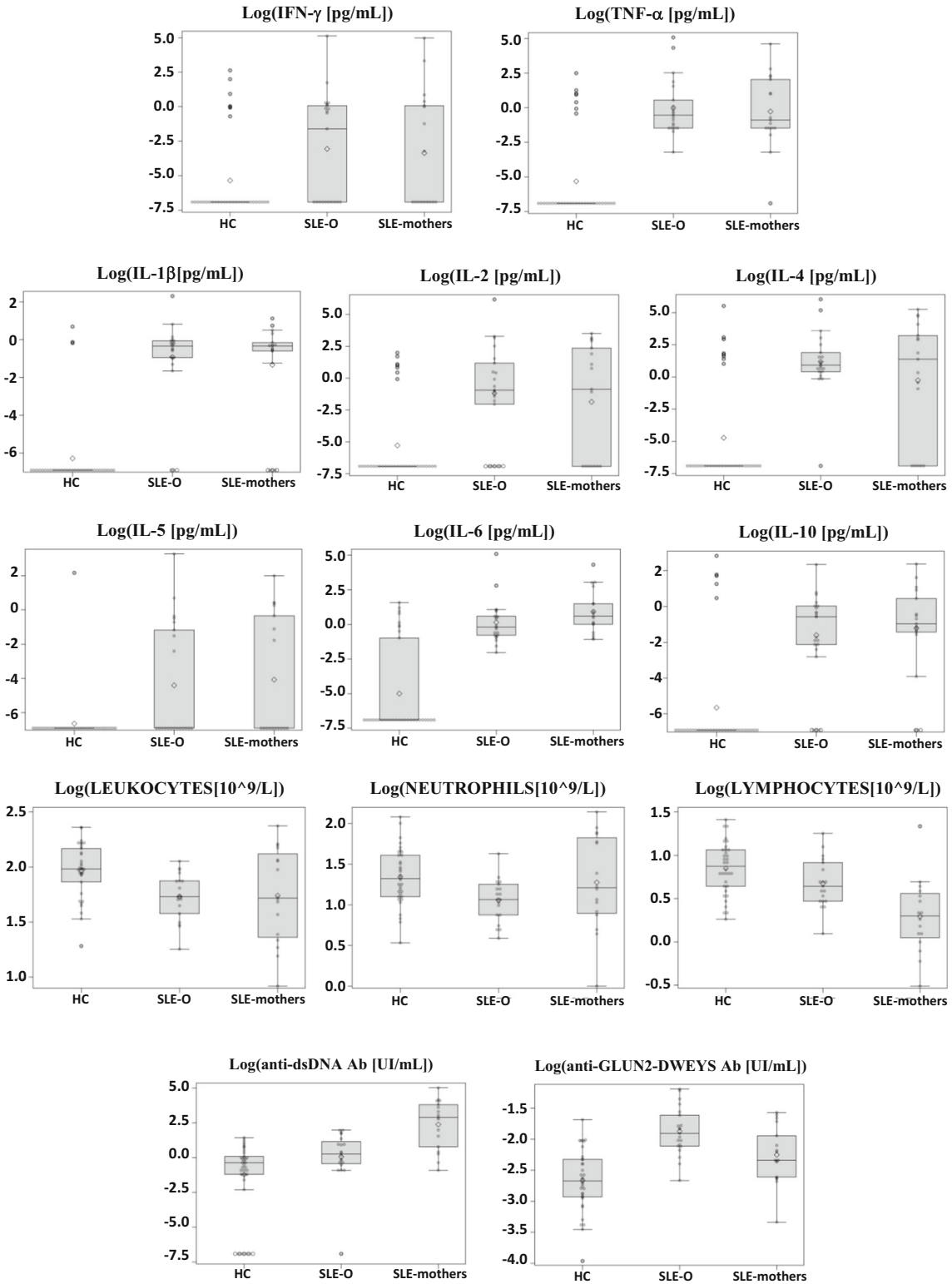

Fig. 1 Immunological results: differences between lupus offspring and healthy controls and comparison with lupus mothers. Graphical comparison of values for cytokines (IFN-g, TNF-a, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-10), anti-GluN2-DWEYS and anti-dsDNA antibodies, and leukocyte, lymphocyte and neutrophil count for healthy controls, and SLE offspring and SLE mothers, respectively. In the box-plot figures, values are transformed into their logarithms, and zero values are imputed to a very small value of 0.001 before the log transformation. The bottom and top edges of the box indicate the intra-quartile range (IQR). The whiskers extending from each box indicate the range of values that fall within a distance from the box less than or equal to 1.5*IQR. Median value is the line within the box, and mean is the rhombus dot. HC = healthy controls; SLE-O = offspring of women with lupus; SLE-mothers = mothers with lupus

Table 4 Significant correlations between depression and stress scales in lupus offspring, and physical and psychopathological ratings in lupus mothers

SLE-O scales	Mothers' scales			
	SLEDAI-pregnancy	SLEDAI-current	SLICC-DI	HADS-depression
Depression (CDI-BDI)	0.594* (0.015)	0.798** (< 0.001)	0.499* (0.049)	0.606* (0.017)
Stressful Life Events—SLES		0.760** (< 0.001)		0.606* (0.017)
Verbal Capacity Index		− 0.709** (0.002)	− 0.585* (0.022)	− 0.632* (0.015)
Working Memory Index			− 0.580* (0.023)	− 0.538* (0.047)
ROCF-Copy Exactness		− 0.633** (0.006)	− 0.557* (0.025)	
CPT-II time of reaction			− 0.516* (0.041)	− 0.521* (0.046)
Text comprehension	− 0.549* (0.028)	− 0.608** (0.010)		

Statistically significant Spearman's rho coefficients (p value) at the 0.05* or at the 0.01** levels

SLE-O = offspring of women with lupus; *CDI* = Child Depression Inventory; *BDI* = Beck Depression Inventory, *SLES* = Stressful Life Events Schedule in children; *ROCF-Copy Exactness* = Rey–Osterrieth complex figure test, measure for exactness of copy; CPT-II time of reaction = Conners' Continuous Performance Test—second edition, time-of-reaction subscale; *SLEDAI-pregnancy* and *SLEDAI-current* = SLE Disease Activity Index reconstructed at pregnancy and current score; *SLICC-DI* = Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index; *HADS-depression* = Hospital Anxiety and Depression Scale—depression subscale

more active during development than in adult life, where titers may increase again during episodes of acute NPSLE decompensations. It is important to note that these SLE patients were in relatively good health, with limited disease activity and accumulated damage, and without signs for acute serious NPSLE.

The high correlations found between offspring measures for depression scale and neurocognitive parameters, with maternal psychophysical condition at test time, are worth commenting on. Several large studies have shown how parental depressive symptoms increase in offspring the overall risk for onset of depressive and externalizing disorders (reviewed in [46]) and how cognitive performance and in particular verbal capacities appear lower in children of mothers with persistent depressive symptoms [47–49]. Potential mechanisms include reduced overall warmth and sensitivity and qualitative and quantitative differences in a variety of specific maternal behaviors that shape cognitive and language development [47]. Even though in our population such effect could partly be counteracted by a stable and supportive familiar structure, and by the mothers' investment and expectations, our results indicate a tight connection between maternal and filial well-being.

The model is summarized in the figure found in the graphical abstract.

Limitations/future developments

The study has various limitations. The sample size of the SLE-O is relatively low, and the study is cross-sectional, which impedes assessing causality of events. Assessment of pregnancy and delivery conditions was run retrospectively from mothers' recollections, and laboratory data about mothers' immune/inflammatory profile and medical treatment during pregnancy were missing. Measure of anti-phospholipid antibodies, repeatedly associated with later development of learning disabilities (reviewed in [1]), was not included in the protocol.

This work was though intended as exploratory and focusing on the offspring immunological and neuropsychological characteristics.

HC were psychopathologically healthy subjects and offspring of mothers without any systemic rheumatic disorders, though not an exactly general population sample. This had though the advantage of comparing SLE-O with "pure" subjects, i.e., subjects free from immune alterations linked to possible comorbid psychopathology and from exposure to maternal immunity and maternal hereditary risk for autoimmune diseases [39].

Conclusions

These results endorse a multifactorial etiology for the development of these offspring, where prenatal maternal factors would combine with intrinsic immune condition and with environmental exposure to maternal psychophysical state and together contribute to the psychoneurological trajectory of this population. The clinical impact on cognition and mental health of the subclinical autoimmunity found in the SLE-O should be investigated in longitudinal studies.

If results are confirmed, approaches targeting the proinflammatory condition as well as intervention aiming to support both mothers and offspring might protect these children toward a sound psychophysical development.

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Compliance with ethical standards

Disclosure None.

List of abbreviations *Ab* , autoantibodies; *ADHD*, attention deficit and hyperactivity disorder; *ANA Ab*, anti-nuclear antibodies; *Anti-DWEYS-GluN2 Ab*, antibodies against the GluN2 subunit of the NMDAR; *anti-RP* Ab, anti-ribosomal P protein antibodies; *aPL* Ab, antiphospholipid antibodies; *ASD*, autism spectrum disorders; *ASLO* Ab, anti-streptolysin-O (ASLO) antibodies; *BBB*, blood brain barrier; *BDI*, Beck Depression Inventory; *BMI*, body mass index; *CBA*, cell based assays; *CDRS-R*, Children's Depression Rating Scale—revised; *HADS*, Hospital Anxiety and Depression; *HC*, healthy controls; *IHC*, immunochemistry; *LD*, learning disabilities; *NMDAR*, *N*-methyl-D-aspartate receptor; *NPSLE*, neuropsychiatric lupus; *OCD*, obsessive-compulsive disorder; *OCS scale*, obstetrical complication scale; *SCARED*, Screen for Child Anxiety Related Emotional Disorders; *SES* scale, socioeconomic status scale; *SLE*, systemic lupus erythematosus; *SLEDAI scale*, SLE Disease Activity Index scale; *SLE-O*, offspring of women with SLE; *SLES-C*, Stressful Life Events Schedule, child version; *SLES-P*, Stressful Life Events Schedule—parent version; *SLICC-DI*, Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index scale; *WAIS-III*, Wechsler adult intelligence scale 3rd edition; *WISC- IV*, the Wechsler intelligence scale for children 4th edition

References

1. Vinet É, Pineau CA, Clarke AE, Fombonne É, Platt RW, Bernatsky S (2014) Neurodevelopmental disorders in children born to mothers with systemic lupus erythematosus. Lupus 23:1099–1104. https://doi.org/10.1177/0961203314541691
2. Lee JY, Huerta PT, Zhang J, Kowal C, Bertini E, Volpe BT, Diamond B (2009) Neurotoxic autoantibodies mediate congenital cortical impairment of offspring in maternal lupus. Nat Med 15:91–96. https://doi.org/10.1038/nm.1892
3. DeGiorgio LA, Konstantinov KN, Lee SC et al (2001) A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. Nat Med 7:1189–1193. https://doi.org/10.1038/nm1101-1189
4. Smith SEP, Li J, Garbett K, Mirnics K, Patterson PH (2007) Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci 27:10695–10702. https://doi.org/10.1523/JNEUROSCI.2178-07.2007
5. (1999) The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 42:599–608. https://doi.org/10.1002/1529-0131(199904)42:4<599::AID-ANR2>3.0.CO;2-F
6. Tay SH, Mak A (2015) Anti-NR2A/B antibodies and other major molecular mechanisms in the pathogenesis of cognitive dysfunction in systemic lupus erythematosus. Int J Mol Sci 16:10281–10300. https://doi.org/10.3390/ijms160510281
7. Couture J, Ben-Shoshan M, Pineau CA, Scott S, Clarke AE, Bernatsky S, Vinet E (2017) Risk of allergic conditions in children born to women with systemic lupus erythematosus. Arthritis Care Res (Hoboken) 70:315–319. https://doi.org/10.1002/acr.23251
8. Couture J, Bernatsky S, Scott S, Pineau CA, Vinet E (2018) Brief report: risk of childhood rheumatic and nonrheumatic autoimmune diseases in children born to women with systemic lupus erythematosus. Arthritis Rheumatol (Hoboken, NJ) 70:1796–1800. https://doi.org/10.1002/art.40570
9. Tincani A, Danieli E, Nuzzo M, Scarsi M, Motta M, Cimaz R, Lojacono A, Nacinovich R, Taddei F, Doria A, Brucato A, Meroni P, Pregnancy Study Group of It (2006) Impact of in utero environment on the offspring of lupus patients. Lupus 15:801–807
10. Steup-Beekman G, Steens S, van Buchem M, Huizinga T (2007) Anti-NMDA receptor autoantibodies in patients with systemic lupus erythematosus and their first-degree relatives. Lupus 16:329–334. https://doi.org/10.1177/0961203307078224
11. Murashima A, Fukazawa T, Hirashima M, Takasaki Y, Oonishi M, Niijima S, Yamashiro Y, Yamataka A, Miyano T, Hashimoto H (2004) Long term prognosis of children born to lupus patients. Ann Rheum Dis 63:50–53
12. el-Roeiy A, Gleicher N, Isenberg D, Kennedy RC, Shoenfeld Y (1987) A common anti-DNA idiotype and other autoantibodies in sera of offspring of mothers with systemic lupus erythematosus. Clin Exp Immunol 68:528–534
13. Lewis SW, Owen MJ, Murray RM (1989) Obstetric complications and schizophrenia: methodology and mechanisms. In: Schulz SCTC (ed) Schizophrenia: a scientific focus. Oxford University Press, Oxford, pp 56–59
14. Murphy TK, Sajid M, Soto O, Shapira N, Edge P, Yang M, Lewis MH, Goodman WK (2004) Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcus in children with obsessive-compulsive disorder and tics. Biol Psychiatry 55:61–68. https://doi.org/10.1016/S0006-3223(03)00704-2
15. Gariup M, Gonzalez A, Lázaro L, Torres F, Serra-Pagès C, Morer A (2015) IL-8 and the innate immunity as biomarkers in acute child and adolescent psychopathology. Psychoneuroendocrinology 62:233–242. https://doi.org/10.1016/j.psyneuen.2015.08.017
16. Bauer M, Goetz T, Glenn T, Whybrow PC (2008) The thyroid-brain interaction in thyroid disorders and mood disorders. J Neuroendocrinol 20:1101–1114. https://doi.org/10.1111/j.1365-2826.2008.01774.x
17. Morer A, Viñas O, Lázaro L, Calvo R, Andrés S, Bosch J, Gastó C, Massana J, Castro J (2006) Subtyping obsessive-compulsive disorder: clinical and immunological findings in child and adult onset. J Psychiatr Res 40:207–213. https://doi.org/10.1016/j.jpsychires.2005.04.003
18. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N (1997) Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36:980–988. https://doi.org/10.1097/00004583-199707000-00021
19. Figueras Masip A, Amador-Campos JA, Gómez-Benito J, del Barrio Gándara V (2010) Psychometric properties of the Children's Depression Inventory in community and clinical sample. Span J Psychol 13:990–999
20. Smucker MR, Craighead WE, Craighead LW, Green BJ (1986) Normative and reliability data for the Children's Depression Inventory. J Abnorm Child Psychol 14:25–39
21. Birmaher B, Khetarpal S, Brent D et al (1997) The Screen for Child Anxiety Related Emotional Disorders (SCARED): scale construction and psychometric characteristics. J Am Acad Child Adolesc Psychiatry 36:545–553. https://doi.org/10.1097/00004583-199704000-00018
22. Williamson DE, Birmaher B, Ryan ND, Shiffrin TP, Lusky JA, Protopapa J, Dahl RE, Brent DA (2003) The stressful life events

schedule for children and adolescents: development and validation. Psychiatry Res 119:225–241
23. Wechsler D (2006) Escala de Inteligencia de Wechsler para Niños, 4a edición. TEA Edicio, Madrid
24. Rey A (1980) Test de la Figura Compleja de Rey. TEA Edicio, Madrid
25. Reynolds C, Bigler E (2001) TOMAL: Test de Memoria y Aprendizaje. TEA Edicio, Madrid
26. Culberston WC, Zillmer EA (2006) Tower of London. Multi-Health Systems Inc, Drexel University (TOLDX), Toronto
27. Conners CK, Staff MHS, Connelly V et al (2000) Conners' continuous performance test II (CPT II V. 5). Multi-Health Syst Inc 29: 175–196. https://doi.org/10.1207/s15326942dn2901_9
28. Cuetos F, Rodríguez B, Ruano E (1996) PROLEC: Batería de evaluación de los procesos lectores de los niños de educación primaria [Evaluation of reading processes of primary education students]. TEA Ediciones, Madrid, Spain
29. Romero-Diaz J, Isenberg D, Ramsey-Goldman R (2011) Measures of adult systemic lupus erythematosus: updated version of British Isles Lupus Assessment Group (BILAG 2004), European Consensus Lupus Activity Measurements (ECLAM), Systemic Lupus Activity Measure, Revised (SLAM-R), Systemic Lupus Activity Questionnaire for Population Studies (SLAQ), Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Arthritis Care Res (Hoboken) 63(Suppl 1):S37–S46. https://doi.org/10.1002/acr.20572
30. Snaith RP (2003) The hospital anxiety and depression scale. Health Qual Life Outcomes 1:29. https://doi.org/10.1186/1477-7525-1-29
31. Ezpeleta L, Guillamón N, Granero R, de la Osa N, María Domènech J, Moya I (2007) Prevalence of mental disorders in children and adolescents from a Spanish slum. Soc Sci Med 64: 842–849. https://doi.org/10.1016/j.socscimed.2006.10.031
32. van der Linden MW, Westendorp RG, Zidane M et al (2001) Autoantibodies within families of patients with systemic lupus erythematosus are not directed against the same nuclear antigens. J Rheumatol 28:284–287
33. Dean GS, Tyrrell-Price J, Crawley E, Isenberg DA (2000) Cytokines and systemic lupus erythematosus. Ann Rheum Dis 59:243–251
34. Yoshio T, Okamoto H, Kurasawa K, Dei Y, Hirohata S, Minota S (2016) IL-6, IL-8, IP-10, MCP-1 and G-CSF are significantly increased in cerebrospinal fluid but not in sera of patients with central neuropsychiatric lupus erythematosus. Lupus. 25:997–1003. https://doi.org/10.1177/0961203316629556
35. Sharif MN, Tassiulas I, Hu Y, Mecklenbrauker I, Tarakhovsky A, Ivashkiv LB (2004) IFN-alpha priming results in a gain of proinflammatory function by IL-10: implications for systemic lupus erythematosus pathogenesis. J Immunol 172:6476–6481
36. Llorente L, Richaud-Patin Y, García-Padilla C, Claret E, Jakez-Ocampo J, Cardiel MH, Alcocer-Varela J, Grangeot-Keros L, Alarcón-Segovia D, Wijdenes J, Galanaud P, Emilie D (2000) Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic lupus erythematosus. Arthritis Rheum 43:1790–1800. https://doi.org/10.1002/1529-0131(200008)43:8<1790::AID-ANR15>3.0.CO;2-2
37. Miller AH, Haroon E, Raison CL, Felger JC (2013) Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress Anxiety 30:297–306. https://doi.org/10.1002/da.22084
38. Stuart MJ, Singhal G, Baune BT (2015) Systematic review of the neurobiological relevance of chemokines to psychiatric disorders. Front Cell Neurosci 9:357. https://doi.org/10.3389/fncel.2015.00357
39. Mitchell RHB, Goldstein BI (2014) Inflammation in children and adolescents with neuropsychiatric disorders: a systematic review. J Am Acad Child Adolesc Psychiatry 53:274–296. https://doi.org/10.1016/j.jaac.2013.11.013
40. Ratnayake U, Quinn T, Walker DW, Dickinson H (2013) Cytokines and the neurodevelopmental basis of mental illness. Front Neurosci 7:180. https://doi.org/10.3389/fnins.2013.00180
41. Skerry TM, Genever PG (2001) Glutamate signalling in non-neuronal tissues. Trends Pharmacol Sci 22:174–181
42. Gono T, Kawaguchi Y, Kaneko H, Nishimura K, Hanaoka M, Kataoka S, Okamoto Y, Katsumata Y, Yamanaka H (2011) Anti-NR2A antibody as a predictor for neuropsychiatric systemic lupus erythematosus. Rheumatology (Oxford) 50:1578–1585. https://doi.org/10.1093/rheumatology/keq408
43. Faust TW, Chang EH, Kowal C, Berlin R, Gazaryan IG, Bertini E, Zhang J, Sanchez-Guerrero J, Fragoso-Loyo HE, Volpe BT, Diamond B, Huerta PT (2010) Neurotoxic lupus autoantibodies alter brain function through two distinct mechanisms. Proc Natl Acad Sci U S A 107:18569–18574. https://doi.org/10.1073/pnas.1006980107
44. Gerosa M, Poletti B, Pregnolato F, Castellino G, Lafronza A, Silani V, Riboldi P, Meroni PL, Merrill JT (2016) Antiglutamate receptor antibodies and cognitive impairment in primary antiphospholipid syndrome and systemic lupus erythematosus. Front Immunol 7:5. https://doi.org/10.3389/fimmu.2016.00005
45. Brunner HI, Klein-Gitelman MS, Zelko F, Beebe DW, Foell D, Lee J, Zaal A, Jones J, Roebuck-Spencer T, Ying J (2014) Blood-based candidate biomarkers of the presence of neuropsychiatric systemic lupus erythematosus in children. Lupus Sci Med 1:e000038. https://doi.org/10.1136/lupus-2014-000038
46. Natsuaki MN, Shaw DS, Neiderhiser JM, Ganiban JM, Harold GT, Reiss D, Leve LD (2014) Raised by depressed parents: is it an environmental risk? Clin Child Fam Psychol Rev 17:357–367. https://doi.org/10.1007/s10567-014-0169-z
47. Sohr-Preston SL, Scaramella LV (2006) Implications of timing of maternal depressive symptoms for early cognitive and language development. Clin Child Fam Psychol Rev 9:65–83. https://doi.org/10.1007/s10567-006-0004-2
48. Conners-Burrow NA, Bokony P, Whiteside-Mansell L, Jarrett D, Kraleti S, McKelvey L, Kyzer A (2014) Low-level depressive symptoms reduce maternal support for child cognitive development. J Pediatr Health Care 28:404–412. https://doi.org/10.1016/j.pedhc.2013.12.005
49. Evans J, Melotti R, Heron J, Ramchandani P, Wiles N, Murray L, Stein A (2012) The timing of maternal depressive symptoms and child cognitive development: a longitudinal study. J Child Psychol Psychiatry 53:632–640. https://doi.org/10.1111/j.1469-7610.2011.02513.x