ORIGINAL ARTICLE

Verbal ability impairment in juvenile systemic lupus erythematosus

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ABSTRACT

Introduction/Objective: Evaluate the frequency of verbal ability impairment and associated factors in patients with juvenile systemic lupus erythematosus (JSLE). **Patients and Methods**: Cross sectional study of 36 children and adolescents with JSLE of a group of 57 patients at the Clinic of Rheumatology, Department of Pediatrics and Medical Clinic of *Santa Casa de Misericórdia de São Paulo*. At the time of diagnosis and study, we analyzed the following epidemiological features: clinical, socioeconomic, and educational level. Patients underwent cognitive and laboratory tests and we assessed disease activity (SLEDAI), cumulative damage (SLICC-DI), and treatment with corticosteroids. The patients underwent cognitive tests (Wechsler Intelligence Scales: WISC III and Waiss III), and the results were evaluated according to epidemiological, clinical, laboratory and treatment features. **Results**: The mean age at diagnosis was 11.2 ± 2 years and at the time of the study the mean age was 15.4 ± 4.7 years. There was predominance of women (89%) and of socioeconomic class C patients (61.1%). The cognitive impairment found in these patients was frequent (58.3%), affecting more often the verbal ability. We found association of verbal ability impairment with low socioeconomic status and cumulative damage ($P < 0.05$), but not with disease activity, presence of autoantibodies, and dose of corticosteroids ($P > 0.05$). **Conclusions**: Change in verbal ability is frequent in JSLE and is associated with socioeconomic status and cumulative damage, and should be suspected and investigated, particularly in pediatric patients to avoid quality of life impairment in adulthood. As it is not related with disease activity or presence of autoantibodies, it should always be assessed in the presence or absence of these factors. Likewise, the doses of corticosteroids should be independently evaluated.

Keywords: systemic lupus erythematosus, cognition, child, adolescent, cognitive tests.

INTRODUCTION

Juvenile systemic lupus erythematosus (JSLE) is a chronic, multisystemic, inflammatory, autoimmune disease, which affects patients younger than 16 years.

Neuropsychiatric involvement is a determinant manifestation of morbidity and mortality in systemic lupus erythematosus (SLE), which includes cognitive impairment with prevalence between 14% and 91%.[1] This wide variation is due to the different criteria used for this impairment diagnosis and different socioeconomic conditions of patients.[1,2]

Since the publication of Carbotti *et al.* (1986), the prevalence of cognitive impairment in SLE began to be analyzed more systematically.[3] In 1999, the American College of Rheumatology (ACR) Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature has developed

definitions for 19 neuropsychiatric syndromes of SLE and made recommendations on clinical, laboratory, imaging techniques, and cognitive tests used in the diagnosis of cognitive dysfunction.[4] ACR Nomenclature and Case Definitions for Neuropsychiatric Lupus Syndromes defined cognitive impairment as a dysfunction of one or more of the following areas: simple or complex attention, memory, visual/spatial processing, language, reasoning, psychomotor speed, and executing functions, proven by tests.[4]

An estimated prevalence of SLE cognitive dysfunction in adults is between 12% and 80%[4-8] and between 22% and 95% in pediatric patients.[9,10] This wide variability is justified by the complexity of defining cognitive impairment and by the clinical and demographic diversity of lupus. The diagnosis of cognitive impairment requires professional expertise, time and expenses, which can hamper its identification.

Cognitive dysfunction is reported in adult SLE patients in isolated cases and small series,[4-8] but there are few studies in patients with JSLE.[9-11]

There is a combination of physical and biosocial factors related to environment and lupus therapy that places the patient at greater risk for developing psychological changes, such as mood change, amplification of prior neurotic problems, and triggering or potentiating preexisting cognitive dysfunction.[12,13]

Lupus cognitive impairment may cause negative impact in school and work activities; however, this situation is not always recognized in clinical practice. This disorder can present with variable intensity and be floating in evolution.[12] It is not generally progressive, except in cases in which antiphospholipid antibodies are present. These patients revealed a more marked impairment of verbal ability.[9,13]

The aim of this study is to assess the frequency of verbal ability impairment and the potential factors that interfere with its onset in patients with JSLE.

PATIENTS AND METHODS

Fifty-seven patients diagnosed with JSLE were followed in rheumatology outpatient clinics of the Pediatrics Department or Medical Clinic of *Santa Casa de Misericórdia de São Paulo* from October 2004 to December 2006.

For inclusion criteria, patients had to meet four or more ACR classification criteria for SLE,[14] have initial age below 16 years (JSLE), and minimum follow-up time of four months from diagnosis to study execution. Exclusion criteria were presence of neurological disorder before the diagnosis of JSLE or refusal to perform the cognitive tests. Thirty-six patients

were enrolled in the study, 11 were excluded for non-adherence, and 10 refused or could not perform the tests.

Clinical and laboratory data were analyzed at the time of the study and diagnosis of SLE, obtained from retrospective records of patients' charts, which included gender, age, mucocutaneous, articular, hematologic, serous, kidney, and nervous system impairment. Serological tests performed at diagnosis at the Central Laboratory of *Santa Casa de Misericórdia de São Paulo* included: detection of autoantibodies (antinuclear antibodies - ANA) by immunofluorescence using as substrate human skin cells Hep-II, anti-DNA double-helix (anti-DNA), and antiphospholipid (anticardiolipin IgG and/or IgM and/or lupus anticoagulant on two occasions, with a mean interval of 12 weeks).

At the time of the study, we evaluated the parents' level of education, family socioeconomic status, current age of the patient, duration of disease, laboratory tests, therapeutic aspects, degree of disease activity, SLE cumulative damage index, and cognitive changes.

The educational level, social class, and family income of parents (number of minimum wages) were evaluated according to criteria of socioeconomic status in Brazil (www.abep.org.br).[20] The criterion for socioeconomic classification of Brazil allows the segmentation of the population into classes (A1, A2, B1, B2, C, D, and E), by a score that considers the possession of certain consumer goods (purchasing power) and the householder level of education. Class A1 corresponds to the highest socioeconomic class and class E the lowest.

Laboratory tests performed at the time of cognitive assessment were: ANA, anti-DNA (by indirect immunofluorescence), anticardiolipin IgG and IgM, and anti-ribosomal P protein (by ELISA and confirmed by immunoblotting), measured at the Rheumatology Laboratory of Medical Investigation (LIM) of *Faculdade de Medicina da Universidade de São Paulo*; and lupus anticoagulant, at the Central Laboratory of *Santa Casa de Misericórdia de São Paulo*.

We calculated the cumulative dose of corticosteroids (oral prednisone and methylprednisolone (MTP) pulse therapy intravenously) administered from diagnosis until the time of the study. Low dose was considered as that equivalent to the physiological dose (up to 5 mg/m^2 body surface/day of prednisone) and, above that, high dose.[17] The time of non-physiological doses used was observed from diagnosis until the time of the study.

SLE degree of activity and cumulative damage were assessed at the time of cognitive tests application by SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) and

SLICC-DI (Systemic Lupus International Collaborating Clinics Damage Index) scales, respectively.[18,19]

Cognitive assessment was based on the application of the Wechsler intelligence scales, considered as the international gold standard. The scale selection was done according to age: WISC-III (Wechsler Intelligence Scale for Children – Third Edition) for the age groups between 6 and 16 years, and 11 months, and WAIS-III (Wechsler Adult Intelligence Scale – Third edition) for patients above 17 years of age, administered individually.[15,16] WISC-III and WAIS-III are cognitive tests standardized and validated for Brazilian children and adolescents. The control group consisted of 590 children and adolescents, who were grouped according to age, from a database of *Faculdade de Psicologia da Universidade Federal de Minas Gerais*.

Wechsler scales are divided into subtests for different capacities and are grouped together to assess verbal skills and execution ability, which combined make up the global scale. For each subtest assessed, a score was rated (raw score), from which the points weighted were obtained and summed to determine the rate factor and the intelligence quotient (IQ).

To describe patient's performance, the results of IQ and factor indices were placed in bands and compared with a normal distribution, resulting in a categorical classification: SR ≥ 130, very superior; IQ between 120 and 129, superior; IQ between 110 and 119, high average; IQs between 90 and 109, average; IQ between 80 and 89, low average (mild cognitive impairment); IQ between 70 and 79, borderline (moderate cognitive impairment); and IQ ≤ 69, extremely low (severe cognitive impairment).

As the study aimed to evaluate the impairment of verbal ability, we focus the evaluation on verbal IQ and factorial verbal index.

The project and its term of informed consent were submitted to the Medical Ethics Committee of *Irmandade da Casa de Misericórdia de São Paulo* and both were approved (Project No. 396/04). All patients or their legal representatives signed informed consent.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 14.0. For univariate statistical analysis, we used the chi-square and Fisher's exact test to compare categorical data; for quantitative variables, we used t-test for independent samples and analysis of variance (ANOVA). We considered the significance level of 0.05.

RESULTS

Thirty-six patients with JSLE were evaluated, 32 (89%) were female. At the time of diagnosis, the mean age of patients was 11.2 ± 2 years, ranging from 6 to 14.6 years. At the time of the study and neuropsychological assessment, patient age was 15.4 ± 4.7 years, ranging from 6 to 25.6 years. The duration of disease was 4.3 ± 0.4 years. In 50% of cases, parents had completed primary school. Regarding the socioeconomic evaluation, we found that most families belonged to lower socioeconomic classes: Class C (61.1%) and D (19.4%), and the remainder being divided as follows: 2.8% of patients belonging to class A and 13.9% to class B1. Regarding socioeconomic status, 61.1% of patients belonged to class C (Table 1).

The most frequent clinical manifestation was mucocutaneous (81%), followed by joint (70%). Renal involvement was present in 64%, hematological in 61%, serositis in 34%, and thromboembolic events in 17% of cases. We observed nervous system involvement in six cases (16%), with four cases of seizures and two cases of behavior disorders.

At the study time, among 36 patients, antiphospholipid antibodies were present in approximately 30%, with a slight prevalence of anticardiolipin antibody IgG. Among patients with impaired verbal ability, 36% had positive antiphospholipid

Table 1

Demographic and socioeconomic aspects of 36 patients with juvenile systemic lupus erythematosus

Female: N (%)		32 (89%)
Age at diagnosis of SLE (years): mean ± DP		11.2 ± 2
Duration of disease (years): mean ± DP		4.3 ± 0.4
Age at neuropsychological assessment (years): mean ± DP		15.4 ± 4.7
Parents' education: N (%)	Elementary school/incomplete	18 (50%)
	Elementary school/complete or high school/incomplete	12 (33.3%)
	High school/complete or Superior/incomplete	5 (13.9%)
	Superior/complete	1 (2.8%)
Socioeconomic classes: N (%)	Class A	1 (2.8%)
	Class B1	1 (2.8%)
	Class B2	5 (13.9%)
	Class C	22 (61.1%)
	Class D	7 (19.4%)

antibodies, and anticardiolipin IgG was positive in 31%. Among patients with involvement of the nervous system, only the two with behavior disorders was positive for antiphospholipid antibody. Anti-DNA was positive in 25%, and anti-ribosomal P was positive in 8% of cases.

Regarding treatment, all patients received corticosteroids, and the average cumulative was 27.3 g (0.5 g to 123.8 g), the dose of corticosteroid administered at the time of cognitive testing ranged from 0-35 mg/day (15 ± 9.4 mg). Treatment duration with corticosteroids in these patients ranged from 2.4 to 158 months (34 ± 35.9 months). The mean total dose administered orally (from the initial use of corticosteroids to the time of cognitive assessment) was 15.4 g ± 13g and the dose administered as an intravenous pulse therapy was 9.7 ± 11.1 g. The average use of corticosteroids administered at a dose above the physiological was 24.7 ± 32.2 months.

Regarding the disease activit, the SLEDA I mean was 4.8 ± 5.3, and the cumulative damage index SLICC-DI was 1.5 ± 1.3.

When comparing control group with patient group, we observed that the mean rate of verbal ability was lower in the second group. In the patient group, the mean prevalence was 88.9 ± 21.3, while in the control group it was 108.5 ± 25.9 (P = 0.01). With regard to age, differences were detected when comparing the control group with the group of patients. When performing a segmentation (patients above and below 10 years), it was observed that the average index assessing verbal ability was lower in patients aged over 10 years.

Cognitive dysfunction occurred in 58.3% of 36 patients. The processing speed was little affected, while the frequency

of impaired verbal ability, executing functions, attention, and concentration were similar. It was not found severe cognitive dysfunction.

Univariate analysis showed no association between verbal ability dysfunction and age at diagnosis or duration of SLE (P > 0.05). Statistically significant difference was found when family income was associated with verbal ability (P = 0.02) (Table 2). There was no association of cognitive dysfunction with autoantibodies: anti-double-stranded DNA, antiphospholipid, and anti-ribosomal P protein (P > 0.05) (Table 3).

The presence of disease activity detected by high SLEDAI did not correlate with verbal ability impairment (P > 0.05), but there was correlation with cumulative damage (SLICC-DI) (P = 0.02) (Table 4).

Verbal ability was not affected by treatment with corticosteroids, either in relation to dose, form of administration, time of drug use, or time of dose higher than physiological (P > 0.05) (Table 4).

DISCUSSION

The clinical manifestations of JSLE neuropsychiatric impairment range from discrete conditions, such as cognitive dysfunction and difficult diagnosis, to psychotic condition. Because it is an important prognostic factor, efforts should be made to diagnose conditions with mild neuropsychiatric manifestations, enabling an early and appropriate treatment in order to improve morbidity and mortality of lupus disease.

Table 2

Impairment of verbal ability and demographics and socioeconomic factors in 36 patients with juvenile systemic lupus erythematosus

| | | Impairment | | |
		Absence	Presence	P
Duration of disease (years): mean ± SD		50.3 ± 63.7	55.7 ± 47.4	0.78
Age at diagnosis of SLE (years): mean ± SD		129.9 ± 21.7	140.5 ± 28.2	0.21
Age at neuropsychological assessment (years): mean ± SD		178.2 ± 56.5	195.8 ± 57.0	0.36
Parent's education (years at school) mean ± SD		7.7 ± 3.2	6.4 ± 2.8	0.21
Socioeconomic class: N (%)	Class A	1 (5%)	0	0.52
	Class B1	1 (5%)	0	
	Class B2	4 (19%)	1 (7%)	
	Class C	12 (57%)	10 (66%)	
	Class D	3 (14%)	4 (27%)	
Family income (number of minimum wages) mean ± SD		2.9 ± 1.2	2.2 ± 0.86	0.02

(ANOVA).

Table 3

Impairment of verbal ability and presence of autoantibodies in 36 patients with juvenile systemic lupus erythematosus

Presence of autoantibodies	Impaired Verbal Ability	
	%	P
Presence of anti-DNA double helix	35.7	0.52
Presence of antiphospholipid antibody	35.7	0.85
Presence of anticardiolipin antibody IgG	30.8	0.82
Presence of anticardiolipin antibody IgM	23.1	0.83
Presence of lupus anticoagulant	23.1	0.66
Presence of anti-ribosomal P protein antibody	13.3	0.51

(Chi-square test).

Table 4

Impairment of verbal ability in lupus and disease activity index (SLEDAI), cumulative damage (SLICC-DI), and use of corticosteroids in 36 patients with juvenile systemic lupus erythematosus

	Verbal Ability		
	Changed	Normal	P
Mean + SD SLEDAI	5.0 ± 5.8	4.5 ± 4.7	0.38
Mean SLICC-DI ± SD	1.7 ± 1.7	1.3 ± 0.7	**0.02**
Current mean dose of corticosteroid (mg)	15.4	15.2	0.63
Mean cumulative dose of corticosteroids (g)	28.0	25.3	0.97
Total dose administered orally (g)	13.4	18.0	0.52
Mean total dose of corticosteroids in pulse therapy (g)	14.6	9.8	0.94
Number of pulses of methylprednisolone	2.7	2.7	0.84
Average length of corticosteroids use (months)	26.2	35.6	0.90
Average length of non-physiological corticosteroids dose (months)	20.5	30.6	0.78
Average duration of disease (months)	46.2	60.8	0.63

SD: standard deviation (ANOVA).

In 1999, with the definition of neuropsychiatric SLE by ACR, it was possible to trace the characterization and diagnosis of impairment, hitherto difficult by the lack of classification criteria and presence of factors that interfere in its manifestations, such as chronic disease and the use of corticosteroids. These facts prevented a more precise establishment of the prevalence of neuropsychiatric involvement in SLE.

The cognitive assessment of patients with JSLE is rarely described in the literature,[9-11] with a predominance of studies in adult populations.[4-8] One of the factors that limit the study in patients with JSLE is the small number of patients, which complicates the implementation of multivariate analysis, requiring the establishment of a multicenter study for better evaluation. This study assessed only pediatric patients, and we observed a frequency of cognitive dysfunction similar to that described in few reports in literature.[10,11] Wyckoff *et al.* (1995) found a lower performance in verbal skills of children with lupus, similar to what happened in our study, in which there was a greater frequency of verbal ability complications.[9] This fact is suggestive of a more complex cognitive function involvement in patients with JSLE.

Since this was a population of lower socioeconomic class and the parents had low education level, one should not dismiss the family influence on patient's cognitive development.[21]

There are reports of association between the presence of antiphospholipid antibodies and cognitive dysfunction.[8,11,13,22] Denburg *et al.* (1997) showed a prevalence of cognitive dysfunction two to three times higher in patients with positive antiphospholipid antibodies, mainly related to verbal memory, cognitive flexibility, and psychomotor speed.[22] Persistent high levels of anticardiolipin IgA are associated with reduction of thinking and executing functions, while high levels of IgG are associated with dysfunction of psychomotor speed.[13] This association was not found by other authors,[23,24] as well as in this study. However, it should be noted that both levels of antiphospholipid antibodies and cognitive dysfunction may be floating. Thus, these possibilities should be evaluated in longitudinal follow-up.[25]

Anti-ribosomal P protein antibodies are associated with neuropsychiatric impairment in SLE, more specifically with psychiatric disorders, lupus psychosis, and depression related to cognitive and psychological changes, suggesting different mechanisms for the various neuropsychiatric manifestations.[25] In the cases evaluated in this study, no association was found between cognitive impairment and presence of anti-ribosomal P protein antibody, but it should be noted the small number of lupus patients with positive anti-ribosomal P protein antibody.

There is controversy about the association between SLE activity and cognitive dysfunction.[7,8,26] It should be remembered that the pathogenesis of cognitive dysfunction is not completely understood, with several factors that may be involved, such as the presence of autoantibodies against nervous system antigens in the absence of systemic activity of disease.

Similar to this study, Carbotti *et al.* found no evidence that the activity of lupus disease itself plays a role in cognitive function in a study correlating activity indices (SLEDAI and LACC) and cognitive impairment.[7] On the other hand, Fisk *et al.* (1993) and Mikdash & Handwerger (2004) found an association between disease activity and recent memory and concentration impairment.[8,26]

Although there is strong correlation between cognitive impairment manifestations and disease activity measures, SLEDAI, and presence of anti-DNA antibodies, it was detected association with the cumulative damage, SLICC-DI, reinforcing the idea that it is a manifestation that can lead to long-term sequelae, emphasizing the importance of detecting this change in childhood. Thus, it would be ideal to follow-up cognitive dysfunction through tests, in order to detect the problem as early as possible and implement measures to reverse these changes. There is controversy about the influence of corticosteroids on cognitive dysfunction. Some studies show this association,[6,8,28,29] whereas others found no such association.[30] The use of corticosteroids in high doses and for prolonged periods can lead to cognitive impairment, as established in literature, particularly related to memory by altering hippocampal function.[29] In this study, both current and cumulative corticosteroid doses, form of administration, or duration of use did not affect verbal ability, similar to other studies in literature.[30]

Due to the small study sample, the association and correlation become impaired and can not be extrapolated to the entire population of patients with JSLE. With this study, we intend to alert professionals who are involved in the care of patients with JSLE for the presence of cognitive impairment and its high frequency.

Thus, we conclude that cognitive impairment, especially of verbal ability, occurs in JSLE, implying the involvement of complex areas. This involvement does not depend on disease activity and does not always correlate with the presence of antibodies, whether neuronal or antiphospholipid, or even with treatment.

This may indicate that changing drug therapy may not be necessary in some cases, but provide neuropsychological support to help these patients to benefit, by adopting measures to stimulate the impaired cognitive domain is necessary in order to avoid difficulties in learning and work, since we are speaking of pediatric patients.

Larger samples and longitudinal assessments are needed to establish a better correlation, which will bring benefit to patients with JSLE.

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