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Original article

Association between academic performance and cognitive dysfunction in patients with juvenile systemic lupus erythematosus

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ARTICLE INFO

Article history:
Received 1 September 2015
Accepted 12 January 2016
Available online 18 April 2016

Keywords:
Juvenile systemic lupus erythematosus
Cognitive dysfunction
Academic performance

ABSTRACT

Objective: To determine whether there is an association between the profile of cognitive dysfunction and academic outcomes in patients with juvenile systemic lupus erythematosus (JSLE).

Methods: Patients aged ≤18 years at the onset of the disease and education level at or above the fifth grade of elementary school were selected. Cognitive evaluation was performed according to the American College of Rheumatology (ACR) recommendations. Symptoms of anxiety and depression were assessed by Beck scales; disease activity was assessed by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI); and cumulative damage was assessed by Systemic Lupus International Collaborating Clinics (SLICC). The presence of autoantibodies and medication use were also assessed. A significance level of 5% ($p < 0.05$) was adopted.

Results: 41 patients with a mean age of 14.5 ± 2.84 years were included. Cognitive dysfunction was noted in 17 (41.46%) patients. There was a significant worsening in mathematical performance in patients with cognitive dysfunction ($p = 0.039$). Anxiety symptoms were observed in 8 patients (19.51%) and were associated with visual perception ($p = 0.037$) and symptoms of depression were observed in 1 patient (2.43%).

Conclusion: Patients with JSLE concomitantly with cognitive dysfunction showed worse academic performance in mathematics compared to patients without cognitive impairment.

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http://dx.doi.org/10.1016/j.rbre.2016.03.005

Associação entre desempenho acadêmico e disfunção cognitiva em pacientes com lúpus eritematoso sistêmico juvenil

Palavras-chave:
Lúpus eritematoso sistêmico juvenil
Disfunção cognitiva
Desempenho acadêmico

RESUMO

Objetivo: Determinar se há associação entre o perfil de disfunção cognitiva e os resultados acadêmicos em pacientes com lúpus eritematoso sistêmico juvenil (LESj).
Métodos: Foram selecionados pacientes com idade de início da doença ≤ 18 anos e com escolaridade mínima do quinto ano do Ensino Fundamental seguidos em um hospital universitário. A avaliação cognitiva foi feita de acordo com as recomendações do Colégio Americano de Reumatologia (ACR). Os sintomas de ansiedade e depressão foram avaliados pelas escalas Beck, a atividade da doença foi avaliada pelo Systemic Lupus Erythematosus Disease Activity Index (Sledai) e o dano cumulativo pelo Systemic Lupus International Collaborating Clinics (Slicc). Também foram avaliados a presença de autoanticorpos e o uso de medicação. Adotou-se nível de significância de 5% ($p < 0,05$).
Resultados: Foram incluídos 41 pacientes com média de $14,5 \pm 2,84$ anos. Disfunção cognitiva foi observada em 17 (41,46%). Observou-se pioria significativa no desempenho de matemática em pacientes com disfunção cognitiva ($p = 0,039$). Sintomas de ansiedade foram observados em oito pacientes (19,51%) e estavam associados à percepção visual ($p = 0,037$) e sintomas de depressão foram observados em um paciente (2,43%).
Conclusão: Pacientes com LESj com disfunção cognitiva apresentam pior desempenho acadêmico em matemática em relação a pacientes sem disfunção cognitiva.

Introduction

Systemic lupus erythematosus (SLE) is a chronic and autoimmune inflammatory disease of connective tissue. Of unknown etiology, SLE is linked to genetic, hormonal, environmental factors, and to the use of some medications. This disease mostly affects women in childbearing age, especially between 15 and 50 years. However, approximately 20% of patients are affected during childhood or adolescence (JSLE), being predominantly of female gender.[1–3]

JSLE patients show a more severe form of the disease and develop neuropsychiatric symptoms at higher frequencies than in adult patients.[4] Cognitive disorders are common and affect mainly attention, concentration, learning, memory, information processing and executive functions, even in the apparent absence of disease activity or of other neuropsychiatric events.[5–8]

Few studies available in the literature suggest that JSLE patients are at risk of poor academic performance,[9,10] especially causing difficulties in arithmetic learning, reading comprehension, visual memory and inability to solve complex problems.[10] For these reasons, patients with SLE can meet fewer educational milestones, for example, not finishing high school or college graduation – factors associated with a lower probability of employment and of success at work.[10–12] In this scenario, the aim of this study was to determine whether there is an association between the profile of cognitive dysfunction and academic outcomes in patients with JSLE.

Materials and methods

Consecutive patients with JSLE seen at the Pediatric Rheumatology Outpatient Clinic, Hospital das Clínicas, Universidade Estadual de Campinas (UNICAMP), whose clinical and laboratory manifestations were routinely studied according to an already established protocol, were selected.[13,14] Inclusion criteria were: patients with age of onset of disease ≤18,[15] and with fifth grade of elementary school as the minimum level of scholarship. The study was approved by the Research Ethics Committee (CEP No. 920/2007) of UNICAMP and all the participants and legal guardians signed an informed consent form (FICF).

Cognitive assessment was performed by a qualified psychologist through the application of a survey battery lasting about two hours, consisting of tests adapted to the juvenile population and validated for the Portuguese language and selected from the battery recommended by the American College of Rheumatology (ACR).[16] The following tests for evaluation of cognitive functions were selected:

- Picture Arrangement Test: evaluates temporal reasoning[17,18]
- Code Test: evaluates processing speed[17,18]
- Picture Completion Test: evaluates visual perception[17,18]
- Cube Test: evaluates spatial reasoning[17,18]
- Digit Test: assesses immediate and working memory[17,18]
- Vocabulary Test: evaluates semantic memory, educational background and general intelligence[17,18]
- Rey Complex Figure Test: evaluates perceptual organization, planning, praxis and memory[19]
- Boston Naming Test: evaluates visual recognition and naming capacity[20]
- FAZ Verbal Fluency Test: assesses verbal-phonological fluency[21]
- Trail Making Test: assesses visual tracking, sustained attention and motor dexterity[22]

- Stroop Neuropsychological Screening Test: evaluates selective attention, inhibitory control and mental flexibility[23]

Each patient had his/her scores counted individually.

Seventy-one controls matched for gender, age and socioeconomic status were included in order to obtain normative data of applied tests. Presence of cognitive impairment has been defined in cases of cognitive function with a mean Z-score ≤−2 SD or two or more functions with a mean Z-score between −1 and −2 SD.[24]

On the day of the cognitive tests, the school report of the last academic semester of each participant was requested. The participants were grouped by discipline: Portuguese/English/Spanish; Geography/History; Physical/Chemical/Biological Sciences; Mathematics; Physical Education; Arts; and Sociology/Philosophy. School grades ≥7 (70% success) were considered as satisfactory.[24–28]

Disease activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) questionnaire and the disease was considered active if the sum of SLEDAI points was >3.[29] Cumulative damage was assessed by the application of a questionnaire specifically developed for this purpose, the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) (SLICC/ACR-DI).[30]

To assess the presence of depressive symptoms, the Children's Depression Inventory – CDI[31] for subjects between 7 and 17 years[32] was applied; this tool is an adaptation of the BDI (Beck Depression Inventory). Anxiety symptoms were assessed using the Beck Anxiety Inventory – BAI.[33,34]

Lab work-up of autoantibodies was carried out; routine techniques used in the Clinical Pathology Laboratory and in the Allergy and Immunology Research Laboratory at Hospital das Clínicas, UNICAMP were used. Antinuclear antibody (ANA) (by indirect immunofluorescence; positive if title >1:40); anti-DNA antibody (by indirect immunofluorescence with *Crithidia luciliae* as substrate)[35]; anti-Smith antibody (by double immunodiffusion); anticardiolipin antibody (by enzyme immunoassay); and lupus anticoagulant (by TTPA and Russell method) were determined.[36] Anti-ribosomal P protein antibody (anti-P) was measured by Enzyme Linked Immuno Sorbent Assay (ELISA).

Medications prescribed on the date of the cognitive tests were taken into account in this study. The drugs were corticosteroids, anti-malarials (chloroquine and hydroxychloroquine), and other immunosuppressive drugs (azathioprine, cyclophosphamide, cyclosporine, methotrexate and mycophenolate mofetil).

Statistical analysis was performed using the Statistical and Graphical Software (Systat) program. Shapiro–Wilk normality test was applied for obtaining results. For statistical analysis, nonparametric Kruskal–Wallis and Fisher's exact test were performed. The significance level was set at 5%, i.e., $p < 0.05$.

Results

Forty-one patients with JSLE (mean age, 14.5 ± 2.84 years), of whom 38 (92.68%) were females, were included and assessed for cognitive impairment and academic notes. Twenty-three (56.09%) patients were elementary education level students, three (7.31%) had completed elementary school and did not continue their studies, and 15 (36.58%) were high school students. The mean age of onset of the disease was 12.58 ± 3.24 years; and the disease duration, until the time of testing, was 2.4 ± 2.63 years. Eleven (26.82%) patients had active disease at the time of testing (mean of SLEDAI, 7.27 ± 2.62).

Table 1 – Demographic, clinical and immunological data of juvenile systemic lupus erythematosus patients with and without cognitive impairment.

Variables	Patients with cognitive dysfunction $n = 17$	Patients without cognitive dysfunction $n = 24$	p-Value
Female	17 (100%)	21 (87.5%)	0.128
Age at diagnosis (mean/SD)	11.47 years (2.47)	13.37 years (3.53)	0.038[a]
Disease duration (mean/SD)	5.11 years (4.21)	7.58 years (4.93)	0.102
Active disease	5 patients (29.41%)	6 patients (28.57%)	0.756
Cumulative damage	3 patients (17.64%)	5 patients (20.83%)	0.75
Anxiety	5 patients (29.41%)	3 patients (12.5%)	0.241
Depression	1 patient (5.88%)	0 patient (0%)	0.235
Anti-P	5 patients (29.41%)	3 patients (12.5%)	0.589
ANA	17 patients (100%)	18 patients (75%)	0.033[a]
Anti-DNA	10 patients (58.82%)	16 patients (66.66%)	0.745
Anti-Smith	7 patients (41.17%)	7 patients (29.17%)	0.430
Anticardiolipin	6 patients (35.29%)	5 patients (20.83%)	0.476
Lupus anticoagulant	6 patients (35.29%)	13 patients (54.16%)	0.342

[a] $p < 0.05$.

The control group was composed of 71 healthy volunteers (90.14% women) with mean age of 16.37 ± 5.21 years. No statistically significant differences were found between patients and controls regarding gender and age, and socioeconomic status. According to the criteria adopted for the definition of cognitive dysfunction, 17 (41.46%) patients and 26 (36.6%) controls had cognitive impairment ($p = 0.08$).

JSLE patients were divided into two subgroups according to the presence or absence of cognitive dysfunction. It was observed that the presence of cognitive impairment was associated with younger age at diagnosis of JSLE ($p = 0.038$) and an association between cognitive impairment and ANA ($p = 0.033$) was noted. Demographic, clinical and immunological data are listed in Table 1.

Symptoms of anxiety were observed in 8 patients (19.51%) and were associated with visual perception ($p = 0.037$), but there was no association of these symptoms with presence

Table 2 – School grades between patients with juvenile systemic lupus erythematosus with and without cognitive impairment.

Discipline	Patients with cognitive dysfunction (mean ± SD)	Patients without cognitive dysfunction (mean ± SD)	*p*-Value
Portuguese/ English/Spanish	7.09 ± 1.29	6.93 ± 1.08	0.302
Geography/History	7.12 ± 1.51	7.38 ± 1.54	0.791
Sciences	6.26 ± 1.52	7.04 ± 1.98	0.195
Physical Education	7.55 ± 1.67	8.04 ± 1.92	0.604
Mathematics	6.68 ± 2.06	7.37 ± 1.65	0.039[a]
Arts	8.14 ± 1.59	8.26 ± 0.98	0.662
Sociology/Philosophy	7.62 ± 1.05	7.14 ± 1.27	0.504

[a] $p < 0.05$.

of cognitive impairment ($p = 0.988$). Symptoms of depression were observed in 1 (2.43%) patient and again there was no association with cognitive impairment ($p = 1.0$). No association was observed between symptoms of anxiety and depression, when compared with academic grades.

No association of cognitive impairment with any medication (corticosteroids, $p = 0.988$; immunosuppressants, $p = 0.75$ and antimalarials, $p = 0.988$) was observed.

When comparing patients with versus without cognitive impairment, school performance showed significant difference between groups only for math grades ($p = 0.039$) (Table 2).

Discussion

In our sample, the frequency of cognitive dysfunction was 41.46%; this finding was consistent with other studies reported in the literature.[4,6,8,24]

The presence of cognitive impairment was associated with poorer performance in mathematics in our patients. Another study found that children with JSLE had poorer academic results versus individuals without this disease.[9] It is suggested that deficits in language ability are among the first markers of presence of neurological disorder in patients with JSLE, and that this difficulty may be present even in patients without neuropsychiatric manifestations.[6] In this study, there was no significant difference in language-related disciplines.

It is a very difficult task to define school performance, in the face of the multiple variables used to assess this phenomenon.[25] Unsatisfactory performance was defined by McCall as the performance of an individual who does not necessarily obtain low grades, but whose grades are below his/her expectations.[26] There is greater consensus in considering as unsatisfactory a performance substantially below expectations for the student's own cognitive ability.[25,26]

It is also difficult to assess school performance, since this parameter depends on different factors, among which are: school physical characteristics, teacher qualifications, education level of parents, and education level of the student.[28] In the literature, several measures are available for evaluation of school performance, including: grade repetition, suspension, grades lower than the expected for the student's coefficient of intelligence, and low grades.[37] In our study, in the definition of poor school performance we considered the occurrence of unsatisfactory notes, i.e. educational achievement <70% for a certain class content.[25–28]

It is known that cognitive dysfunction is associated with high morbidity in patients with JSLE.[5,12] However, a major obstacle to understanding the neuropsychological functioning of these patients is the lack of a standardized criterion for the identification of this dysfunction.[8,24]

The cognitive impairment evaluation consisted of tools adapted to juvenile age group and selected from the battery suggested by ACR[16] for evaluation of cognitive dysfunction in adults, and also with batteries used in recent studies in patients with JSLE.[4,6,8,9,24]

In this study, we found no evidence that disease activity plays a role in cognitive function. This finding is supported by two recently published pediatric studies, in which the authors found no association between disease activity and cognitive dysfunction.[4,8] On the other hand, when individuals with more severe conditions, e.g., hospitalized patients, were included, we could observe an association between disease activity and cognitive dysfunction.[12]

Other authors found no association between cognitive deficit and cumulative damage[38] or medication,[39] which was confirmed in our study.

In children, reports of an association of autoantibodies with cognitive impairment are sparse and inconclusive; moreover, such studies also did not identify in their sample a direct association between the presence of antibodies and cognitive dysfunction.[4,8] However, in our study we found an association with ANA and cognitive impairment, suggesting that there is a link between autoimmunity and cognitive functioning.

It is known that living with a chronic disease can cause major adaptive problems associated with emotional distress, such as irritability, insomnia, loss of appetite, emotional instability, and changes in memory and concentration, which may be reflected in school performance.[27,28,40] For this reason, some authors point out behavior difficulties as a risk factor for poor academic performance of individuals with JSLE.[8,11,41] Behavior difficulties, although being a variable not evaluated in this study, are important in patients with chronic disease, especially in adolescents; these factors may have had some bearing on the results.

Although cognitive disorder frequency has been compared against healthy individuals, unfortunately we did not compute the academic performance of these controls for comparison.

In conclusion, patients suffering from JSLE and with cognitive impairment exhibit a worse academic performance in math, compared to JSLE patients without cognitive impairment.

Funding

Fundação de Amparo à Pesquisa do Estado de São Paulo – Brazil (FAPESP 2008/02917-0 and 2011/03788-2), Conselho Nacional de Pesquisa e Desenvolvimento – Brazil – CNPq (300447/

2009-4 and 471343/2011-0 and 302205/2012-8; and CNPq 473328/2013-5, 466715/2014-5).

Conflicts of interest

The authors declare no conflicts of interest.

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