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ORIGINAL ARTICLE

Uveitis in childhood-onset systemic lupus erythematosus patients: a multicenter survey

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Abstract The aim of this study is to assess uveitis prevalence in a large cohort of childhood-onset systemic lupus erythematosus (cSLE) patients. A retrospective multicenter cohort study including 852 cSLE patients was performed in ten pediatric rheumatology centers (Brazilian cSLE group). An investigator meeting was held and all participants received database training. Uveitis was diagnosed through clinical assessment by the uveitis expert ophthalmologist of each center. Patients with and without uveitis were assessed for lupus clinical/laboratory features and treatments. Uveitis was observed in 7/852 cSLE patients (0.8%). Two of them had ocular complications: cataract and irreversible blindness in one patient and retinal ischemia with subsequent neovascularization and unilateral blindness in another. Uveitis was identified within the first 6 months of cSLE diagnosis in 6/7 patients (86%). Comparison of a subgroup of cSLE patients with (n = 7) and without uveitis (n = 73) and similar length of disease duration showed that patients with uveitis had increased SLEDAI-2K score (19 vs. 6; $p < 0.01$). In addition, fever (71 vs. 12%; $p < 0.01$), lymphadenopathy (29 vs. 1.4%; $p = 0.02$), arthritis (43 vs. 7%; $p = 0.02$), and use of intravenous methylprednisolone (71 vs. 22%; $p = 0.01$) were higher in cSLE patients with uveitis, as compared to those without this manifestation, respectively. Presence of fever was significantly associated with uveitis, independently of SLEDAI scores or use of intravenous methylprednisolone pulses, as shown by adjusted regression analysis (adjusted prevalence ratio 35.7, 95% CI 2.4–519.6; $p < 0.01$). Uveitis was a rare and initial manifestation of active cSLE patients. Early recognition is essential due to the possibility of irreversible blindness.

Keywords Childhood-onset systemic lupus erythematosus · Cohort study · SLEDAI · Uveitis

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, which involves the interaction of genetic, hormonal,

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environmental, and infectious factors. The pathogenesis of SLE is still poorly understood; however, loss of self-tolerance, with production of autoantibodies, formation of immune complexes, increased inflammatory response, and tissue damage, appears to be a major feature of the disease [1–3].

Ocular involvement occurs in approximately one third of adult lupus patients. Several ocular structures may be involved, including the periorbital region, adjacent eye structures, uveal tract, and orbit and optic nerve. Keratoconjunctivitis sicca is the most common ocular manifestation while the involvement of the optic nerve and retinal vessel occlusion are the most severe manifestations, and if not treated early and properly, it may lead to irreversible blindness [4–6].

Uveitis is a term that encompasses many ocular inflammatory diseases, classically characterized by inflammation of the uveal tract, which includes the iris, ciliary body, and choroid, but it can also affect the adjacent structures (sclera, cornea, vitreous body, retina, and optic nerve) due to proximity of the uveal tract [7, 8]. In the USA and Europe, approximately 5 to 20% of cases of uveitis progress to blindness [9].

Presence of uveitis is rare in SLE [10]. Anterior uveitis is less frequent and rarely occurs as an isolated ocular manifestation, whereas SLE is most commonly associated with posterior involvement or with scleritis [6]. A previous retrospective study conducted in one of the participating centers evaluated ocular manifestations in 117 children with SLE without any uveitis report [11].

There are few reports in the literature of uveitis in lupus patients. Almeida et al. (2011) [12] reported two childhood-onset systemic lupus erythematosus (cSLE) patients with irreversible blindness due to retinal vasculitis and severe uveitis. Barisani-Asenbauer et al. (2012) [7] observed that in patients with uveitis followed at the Uveitis Clinics of the Department of Ophthalmology at the Medical University of Vienna, only 7/2619 (0.27%) had a diagnosis of SLE.

Limited research evaluating uveitis prompted the development of this multicenter survey in Brazilian patients with cSLE. Early identification of uveitis in these patients could prevent complications that may lead to irreversible blindness. Therefore, the objective of this study was to assess uveitis in a large cSLE population evaluating its prevalence, clinical characteristics, treatment and outcome.

Materials and method

Study procedure and patient selection

This was a retrospective, multicenter cohort study (Brazilian cSLE group) including 1017 cSLE patients followed in ten pediatric rheumatology tertiary referral services of São Paulo state, Brazil. The period of enrollment of the patients was from January 1983 to October 2014. One hundred and sixty-five patients were excluded as previously described [13]. Therefore, the study group comprised 852 cSLE patients. All patients fulfilled the ACR lupus criteria [14], with disease onset before 18 years of age and current age ≤ 25 years.

An investigator meeting was held for this study on September 29th, 2012, in São Paulo city to define the protocol and to standardize clinical, laboratory, and treatment parameter definition; disease activity; and damage tools scoring. Investigators in each center conducted data collection locally and a unique database was build up. One or more rounds of queries for accuracy sorted out data discrepancy. Data were collected between November 2012 and October 2014.

Patient's medical charts were carefully reviewed according to an extensive standardized protocol for demographic data; lupus-related clinical, laboratorial, therapeutic, and outcome data; and uveitis clinical characteristics, treatments, and outcomes. The frequency of uveitis was determined in the 852 cSLE patients. Subsequently, in order to identify possible associations of uveitis with lupus clinical, laboratory, and treatment features, patients were divided into two groups: with and without uveitis, and were evaluated at comparable length of disease duration.

Routine ophthalmic examination for all cSLE patients was performed by an ophthalmologist with experience in the field in each of the ten pediatric rheumatology centers, at the diagnosis of cSLE and at least once a year, and consisted of slit lamp examination and fundoscopy. Patients with ocular abnormalities due to infections, drugs, or hypertension were not considered for this analysis. The definition, characteristics, and classification of anatomical localization of uveitis were determined based on the Standardization of Uveitis Nomenclature (SUN) criteria [8].

Data related to uveitis surveyed from patient charts were age at onset of uveitis, affected eye, signs and symptoms, disease duration up to the onset of uveitis, anatomic classification of uveitis, description of alterations detected by the ophthalmologist, complications, presence of blindness, and treatment performed (local or systemic). Bilateral blindness was defined as presenting visual acuity (VA) <20/200 in the better-seeing eye. Unilateral blindness was defined as presenting VA ≥20/200 in the better-seeing eye and <20/200 in the worse-seeing eye [15].

Demographic data and clinical evaluation, disease activity, disease damage, and therapies

Descriptors and definitions of SLE Disease Activity Index 2000 (SLEDAI-2 K) were used to score disease activity [16] and custom definitions were previously described [13]. Neuropsychiatric lupus included 19 syndromes according to the ACR classification criteria [14]. Antiphospholipid syndrome was diagnosed according to the current criteria for the classification of pediatric antiphospholipid syndrome [17].

Laboratorial assessment included complete blood cell count, serum urea and creatinine, urinalysis, and 24-h urine protein excretion. Complement levels (CH50, C3, and C4) and anti-double-stranded DNA (anti-dsDNA) autoantibodies were carried out at each center. Cutoff values were considered abnormal according to assay manufacturer. SLE disease activity and cumulative damage were scored through the SLE Disease Activity Index 2000 (SLEDAI-2K) [16], which may range from 0 to 105, and the Systemic Lupus International Collaborating Clinics/ACR-Damage Index (SLICC-ACR/DI) [18], ranging from 0 to 47, respectively.

Current therapy (prednisone, intravenous methylprednisolone pulse, chloroquine diphosphate, hydroxychloroquine sulfate, methotrexate, azathioprine, cyclosporine, mycophenolate, intravenous cyclophosphamide, intravenous gamma globulin, and rituximab) was also recorded.

The Committee for Research Ethics of each center approved the study.

Statistical analysis

Results are presented as number (%) for categorical variables and median (range) for continuous variables. Comparisons of categorical variables were assessed by Fisher's exact test. Continuous variables from cSLE patients with and without uveitis were compared by the Mann-Whitney test. Prevalence ratios (PR) and 95% confidence intervals (95% CI) were estimated by log-binomial regression models using SAS 9.3 software. The significance level was set at 5% for all analysis.

Results

Uveitis was observed in 7/852 (0.8%) cSLE patients and the median duration of the uveitis episode was 5 (4–7) months. The current age at onset of uveitis was 10 (8–14) years. Uveitis was identified at the time of cSLE diagnosis in four patients (57%), during the first 6 months of disease in two patients, and after the first 2 years of follow-up in only one patient. Table 1 describes clinical and follow-up characteristics of the seven cSLE patients with uveitis. Only in one case (patient 2), uveitis was characterized as inactive by the ophthalmologist.

Five of the seven patients (71%) presented uveitis reported symptoms (red eyes, blurred vision, or visual impairment). Four patients (57%) presented posterior uveitis, two had mild bilateral anterior uveitis (29%), and one presented bilateral panuveitis, described as the presence of intense inflammation in the anterior chamber (grade 4+ cells), vitreous, and retina (severe vasculitis). The main changes observed in those with posterior uveitis were the presence of exudates and hemorrhages in choroid (four cases), followed by retinal hemorrhages (one case) and narrowing of retinal vessels (one case).

Two patients presented uveitis complications: one patient had cataracts and bilateral irreversible blindness (patient 4, Table 1), and the other presented retinal ischemia, retinal neovascularization, and unilateral blindness, with final visual acuity of 20/1200 on his right eye and 20/32 on his left eye (patient 6, Table 1). Another patient died 1 month after the uveitis diagnosis due to complications of cSLE (patient 7, Table 1). The remaining four patients evolved to cure without sequelae. Specific treatment for uveitis was used in two patients: topical corticosteroids and mydriatic drops in one and laser therapy in the second one. In the remaining five patients, treatment of lupus was not modified by the presence of uveitis (Table 1).

In order to identify possible associations of uveitis with lupus clinical, laboratory, and treatment features, we compared patients with and without uveitis, evaluated at comparable length of disease duration. Patients with uveitis were evaluated at the time uveitis was diagnosed: six patients within the first 6 months of cSLE onset, and one patient after 31 months of the onset of cSLE symptoms. The group without uveitis included all 64 cSLE patients with disease duration of 0 to 6 months and all nine patients with disease duration of 31 months, with a proportion of approximately 1:10 patients with and without uveitis, respectively. This analysis showed that patients with uveitis had increased SLEDAI-2K score (19 vs. 6; $p = 0.009$). In addition, fever (71 vs. 12%; $p = 0.001$), lymphadenopathy (29 vs. 1.4%; $p = 0.02$), arthritis (43 vs. 7%; $p = 0.02$), and use of intravenous methylprednisolone use (71 vs. 22%; $p = 0.01$) were significantly higher in cSLE patients with uveitis compared to those without this manifestation, respectively (Tables 2 and 3). Adjusted regression analysis revealed that the presence of fever was significantly associated with uveitis, independent of SLEDAI scores or use of intravenous methylprednisolone pulses (PR 35.7; 95% CI 2.4–519.6; $p = 0.009$).

Discussion

Uveitis prevalence in Brazilian cSLE patients who received care at tertiary pediatric rheumatology centers in the State of São Paulo was 0.8%, which confirms that uveitis is a rare manifestation in children and adolescents with SLE. We could not find any published studies which specifically addressed the prevalence of uveitis in adult patients with SLE or in cSLE. Previous studies are limited to case reports or case series [12]. Recently, Donnithorne et al. [19] described two Afro-American girls with cSLE who developed retinal vasculitis.

On the other hand, a retrospective analysis of uveitis etiology in 269 patients younger than 16 years old referred to an

Table 1 Characteristics of patients with childhood-onset systemic lupus erythematosus (cSLE) presenting with uveitis

Characteristics	Patients						
	1	2	3	4[a]	5	6	7
Age at cSLE diagnosis (years)	14	8	9	10	14	14	10
Anatomic classification of uveitis	Anterior	Posterior	Anterior	Panuveitis	Posterior	Posterior	Posterior
Antiphospholipid antibody test	Negative	Negative	ACA IgM	Negative	Negative	ACA IgM/IgG	Negative
Signs and symptoms	Red eyes	None	Red eyes	Red eyes, blurred vision	Red eyes, blurred vision	Blurred vision	None
Duration of SLE up to uveitis (months)	0	6	0	2	31	0	0
Complication	None	None	None	Yes[b]	None	Yes[c]	None
SLEDAI-2K	15	11	19	39	NM	18	32
Specific uveitis treatment	Topic CE; mydriatics	No	Topic CE; mydriatics	Topic CE; mydriatics	No	Laser therapy (retina)	No
Current therapy	NSAIDs	CE, CQ	CE, AZA	CE, MTX	CE	CE, CQ CYF	CE, CYF

cSLE childhood-onset systemic lupus erythematosus, *CE* corticosteroids, *CQ* chloroquine, *AZA* azathioprine, *MTX* methotrexate, *CYC* cyclophosphamide, *ACA IgM/IgG* anticardiolipin IgM and IgG antibodies, *SLEDAI-2K* Systemic Lupus Erythematosus Activity Index 2000, *RE* right eye, *LE* left eye, *NM* not measured

[a] Published by [19]

[b] Cataracts and irreversible blindness

[c] Retinal ischemia and neovascularization with SLE diagnosis

Table 2 Demographic data, clinical manifestations, hematological abnormalities, complement levels, autoantibodies, and disease activity score in 80 childhood-onset systemic lupus erythematosus (cSLE) patients with and without uveitis with similar disease duration

Variables	With uveitis (n = 7)	Without uveitis (n = 73)	p
Demographic data			
Female gender	6 (86)	67 (92)	0.480
Non-Caucasian, n = 73	2 (28.6)	16/66 (24.2)	1.000
Disease duration, (months)	2 (0–31)	4 (0–31)	0.160
Current age, (years)	10.4 (8.8–14.5)	12.5 (3.2–20)	0.250
Clinical manifestations			
Fever	5 (71)	9 (12)	*0.001*
Lymphadenopathy, n = 79	2 (29)	1/72 (1.4)	*0.020*
Arthritis	3 (43)	5 (7.0)	*0.020*
Serositis	1 (14)	12 (8.2)	0.490
Neuropsychiatric involvement	0 (0)	7 (9.6)	1.000
Nephritis	5 (71)	26 (36)	0.100
Antiphospholipid syndrome, n = 77	1 (14)	0/70 (0)	0.104
Laboratory			
Autoimmune hemolytic anemia	1 (14)	8 (11)	0.580
Leukopenia <4000/mm^3, n = 78	1 (14)	10/71 (14)	1.000
Lymphopenia <1500/mm^3, n = 78	1 (14)	16/71 (22)	1.000
Thrombocytopenia <150,000/mm^3, n = 79	2 (28)	10/72 (14)	0.280
Low C3, C4, and/or CH50, n = 62	5 (71)	19/55 (40)	0.220
Autoantibodies			
Anti-ds-DNA, n = 67	4 (57)	23/60 (38)	0.420
Lupus anticoagulant, n = 26	0/4 (0)	4/22 (18)	1.000
Anticardiolipin IgM, n = 29	2/5 (40)	4/24 (17)	0.270
Anticardiolipin IgG, n = 30	1/5 (20)	4/25 (16)	1.000
Disease activity			
Current SLEDAI-2K, n = 73	*19 (11–39)*	*6 (0–41)*	*0.009*

Results are expressed in median (range) or n (%). Values in italic indicate presence of significant statistical differences between patients with and without uveitis

SLEDAI-2K Systemic Lupus Erythematosus Disease Activity Index 2000

Table 3 Current therapy in 80 childhood-onset systemic lupus erythematosus (cSLE) with and without uveitis and similar disease duration

Variables	With uveitis (n = 7)	Without uveitis (n = 73)	p
Prednisone	6 (85)	65 (89)	0.580
Current dose, mg/kg/day, n = 67	0.73 (0.2–2.0)	0.6 (0.05–3.0)	0.690
Intravenous methylprednisolone	5 (71)	16 (22)	*0.010*
Antimalarial drugs, n = 79	2 (28)	46/72 (63)	0.100
Azathioprine, n = 79	1 (14)	21/72 (29)	0.660
Methotrexate	1 (14)	7 (9)	0.540
Mycophenolate mofetil	0 (0)	2 (3)	1.000
Cyclophosphamide, n = 79	2 (28)	5/72 (7)	0.110

ophthalmological tertiary center found only one case of lupus [20], and a recent review of studies on the prevalence of SLE in patients with uveitis [21] reported rates varying from 0.1 to 4.8%. A prospective study of patients presenting with uveitis at an ophthalmology reference center in São Paulo, Brazil, including 15.3% of patients younger than 18 years old, showed that SLE was identified as the cause of uveitis in 14 out of 1053 (1.33%) patients. The main etiology of uveitis in this center was toxoplasmosis (24.03%) [22].

One strength of the present study, considering that uveitis is known to be a rare manifestation of SLE, is the fact that it includes a large number of patients who received care at referral centers of pediatric rheumatology, using a standardized database, which minimizes possible bias. However, it has limitations common to a retrospective study, based on a survey of medical records, with the possibility of incomplete data. Also, although we aimed to use the SUN criteria to classify uveitis, charts from patients seen prior to 2005 did not contain the standardized classification.

In the present study, we observed that uveitis manifestations occurred as one of the presenting features of cSLE in more than half of the cases. In addition, nearly all patients had concomitant systemic disease, reinforcing the concept that the uvea is a target tissue in cSLE. Association of retinopathy and lupus flare has been reported in adult and cSLE patients from Egypt, and adult SLE patients from Japan [23, 24].

Anatomically, posterior uveitis was more often observed, in spite of the fact that lupus was not reported to have a predilection for either anterior or posterior segment of the eye [25, 26].

Uveitis therapeutic choices depend on clinical manifestations of the disease and prognosis and often require continuous suppression of the inflammatory process until remission of the disease is achieved [9]. Since ocular manifestations tend to occur in patients who have active systemic disease, as observed in the present study, proper control of the underlying disease may contribute to the control of ocular manifestation [10].

Of note, eye complains varying from red eyes to blurred vision were present in all but two patients and the initial clinical symptoms were not predictive of severe ocular morbidity. Approximately one third of the patients presented irreversible blindness as consequence of panuveitis or posterior uveitis. A previous study performed in London [27] showed that visual loss occurred in 17% of pediatric patients with uveitis due to different causes (idiopathy, infections, and systemic diseases). Twenty-five percent of the patients with posterior uveitis evolved to blindness, while 3% of patients with acute anterior uveitis and 17% of patients with chronic anterior uveitis showed total loss of vision. Indeed, one of the main concerns in patients with uveitis is vision loss due to severe inflammatory reaction and its complications. Uveitis is considered the leading cause of blindness in the reproductive age group, followed only by diabetes and glaucoma [28]. Despite its low frequency in children, uveitis is a severe condition that has great potential for long-term complications which may lead to blindness [29].

In conclusion, uveitis was a rare and initial manifestation of active cSLE in our large multicenter study. Uveitis in these patients involved more often the posterior segment of the eye, and ocular manifestations varied from asymptomatic to blurred vision. Severity of the initial symptoms was not predictive of visual loss emphasizing the relevance of a specific surveillance for early diagnosis and prompt management.

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