Ocular changes due to the treatment of juvenile systemic lupus erythematosus

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ABSTRACT

Objective: To assess retrospectively the ocular changes in children and adolescents with juvenile systemic lupus erythematosus (JSLE) in a tertiary pediatric rheumatology service. **Methods:** This study assessed 117 JSLE patients (85.5% female, 60.7% non-Caucasian), who met at least four criteria of the 1997 SLE classification of the American College of Rheumatology. Their mean age was 10.4 years, and their mean time of disease progression was 5.4 years. A protocol containing clinical and demographic data, ophthalmologic complaints and changes, age of onset, duration of medication use, and cumulative medication dose was applied. **Results:** Of the 117 patients, 24 (20.5%) had ocular changes. Sixteen of them had abnormal fundoscopy associated with systemic hypertension and/or use of chloroquine; four had cataract; two had glaucoma; and two had cataract and glaucoma. The mean age of ocular change onset was 14.1 years. Patients with ocular changes received statistically higher and longer doses of glucocorticoid pulse therapy as compared with patients without ocular changes [1.5 (0.4 to 1.6) versus 1 (0.2 to 1.6) mg/kg, P = 0.003; 25.7 (2–99) versus 17.8 (1–114) months, P = 0.0001, respectively]. **Conclusion:** A high prevalence of ocular changes relating mainly to the treatment of JSLE was observed. This demonstrates the need for regular ophthalmologic examinations even in asymptomatic patients, aiming at the early diagnosis and intervention, and at decreasing the ocular morbidity related to that disease.

Keywords: autoimmune diseases, eye, glucocorticoids, adolescent.

INTRODUCTION

Juvenile systemic lupus erythematosus (JSLE) is a chronic multisystem inflammatory disease, of unknown etiology and autoimmune nature, which begins before the age of 18 years, but rarely before the age of five years. The disease may be present in all races. During childhood, girls are 4.5 times more affected than boys.[1–4] Of all JSLE cases, 15%–17% develop in the childhood.[5,6]

The criteria for SLE classification suggested by the American College of Rheumatology[7] in 1982 and reviewed in 1997 are used for the diagnosis of SLE.[8]

Several drugs have been used to treat JSLE, mainly glucocorticoids, hydroxychloroquine/chloroquine diphosphate and immunosuppressive drugs, such as azathioprine, cyclosporine, cyclophosphamide, and mycophenolate mofetil.

Any part of the eye or visual system may be affected by thrombotic or inflammatory processes. The eye disease may be asymptomatic or lead to blindness, and there may be no relationship between the ophthalmologic manifestations and disease activity. Ophthalmologic manifestations of SLE may vary from the mucocutaneous disease of the eyelids to the retinal vascular disease and neuro-ophthalmic involvement.[9–12] Scleritis, episcleritis, anterior uveitis, and dry eye are some of the ophthalmologic disorders in SLE.

SLE manifestations detected from observation of the eye fundus usually consist of cotton wool spots with or without intraretinal hemorrhages, papilledema, retinal hyperemia and edema, which may occur even in the absence of intracranial hypertension.[13] Occlusion of large arterioles by spasm and thrombosis has also been described, and occurs in association with vasculitis.[12]

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In addition to the typical ophthalmologic manifestations of the disease, there are those resulting from the use of medications or from disease complications, such as arterial hypertension or thromboembolic disease.

This study aimed at assessing the changes detected on the ophthalmologic examination of JSLE patients, and their relationships with the specific treatment for the disease.

MATERIAL AND METHODS

This study assessed the medical records of 117 patients followed up from 1994 to 2009 and diagnosed with JSLE in accordance with the American College of Rheumatology criteria for SLE classification of 1982[7] and reviewed in 1997.[8] Their clinical and demographic characteristics and their therapy data were assessed. The inclusion criteria comprised all patients with complete and available medical records, whose disease lasted at least six months. A protocol containing clinical and demographic data, systemic involvement, associated diseases, ophthalmologic complaints and changes, age of onset, duration of medication use, and cumulative glucocorticoid dose was applied.

Disease activity was measured by use of the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K).[14] Cumulative damage of the disease was evaluated by use of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus (SLICC/ACR-DI).[15]

The patients of this study underwent ophthalmologic examination at the department of ophthalmology of the same institution every six months. Ophtalmologic examination consisted of the visual acuity test, biomicroscopy to evaluate the ocular surface, tonometry, and indirect binocular ophthalmoscopy. In some cases, when indicated, campimetry was performed.

Patients were considered hypertensive when their medical records showed systolic and/or diastolic blood pressure levels equal to or greater than p95 of the blood pressure table according to gender, height, and age on three or more occasions.[16] The presence of the anticardiolipin antibody was recorded.

To assess the association between dichotomous variables, the chi-square test was used. Continuous variables underwent the Kolmogorov-Smirnov test. To compare both groups, the Student *t* test was used for parametric variables, and the Mann-Whitney test was used for the non-parametric ones. The significance level adopted was 5% ($P < 0.05$).

The study was approved by the ethics committee of Universidade Federal de São Paulo.

RESULTS

Of the 117 patients evaluated, 85.5% were female and 60.7% non-Caucasian. The mean age at the time of evaluation was 10.4 years. The mean time required for the diagnosis of JSLE was 9.9 months, and the mean follow-up time of the disease was 5.4 years.

Of the 117 patients, 24 (20.5%) had ocular changes at some point of their clinical follow-up as follows: 16 had abnormal funduscopy; four had posterior subcapsular cataract; two had glaucoma; and two had glaucoma and posterior subcapsular cataract. Of those 24 patients, 21 (87.5%) were female and 16 (66.7%), non-Caucasian. Their mean age at the time of the JSLE diagnosis was 11.4 years, and the time required for the JSLE diagnosis varied from 1 to 22 months (mean of 4.7 months). Patients' age at the ocular change onset ranged from 5 to 16.2 years (mean of 14.1 years).

When the ophthalmologic manifestation was diagnosed, the mean SLEDAI-2K was 4.2 (ranging from 0 to 23) and the mean SLICC/ACR-DI was 1 (ranging from 0 to 3).

Clinical and demographic data of patients with and without ocular changes are shown in Table 1.

Four out of the 24 patients (16.7%) had ophthalmologic complaints as follows: two (8.3%) reported ocular hyperemia;

Table 1
Clinical and demographic data of JSLE patients (n = 117) with or without ocular change

JSLE	Without ocular change	With ocular change	P
Female gender	79 (84.9%)	21 (87.5%)	NS
Non-Caucasian	55 (59.1%)	16 (66.7%)	NS
Age on the occasion of ocular change (years) (minimum-maximum)	—	14.1 (5–16.2)	
Duration of disease (years) (minimum-maximum)	5 (0.2–14)	5.8 (0.6–13.8)	NS
Patients using GC	9 (100%)	24 (100%)	
Maximum GC dose (mg/kg)	1 (0.2–1.6)	1.5 (0.4–1.6)	0.003*
Duration of GC treatment (months)	27.8 (1–107)	29 (3–103)	NS
Patients on GC pulse therapy	74 (79.6%)	20 (83.3%)	NS
Mean duration of pulse therapy (months)	17.8 (1–114)	25.7 (2–99)	0.000§
Patients on chloroquine	93 (100%)	24 (100%)	—
Patients on other immunosuppressive drugs	66 (70.9%)	13 (54%)	NS
Total of patients	93	24	—

GC: glucocorticoid; NS: non-significant ($P > 0.05$).
*Student *t* test. §Mann-Whitney test.

one (4.2%) reported eye pruritus; and one (4.2%) reported a pricking sensation in the eyes.

Of the 24 patients with ocular changes, seven (29.1%) had positive anticardiolipin antibody titers as follows: two had cataract; one had glaucoma; one had papilledema; and three had macula change. None of those patients had antiphospholipid antibody syndrome.

The age of cataract onset ranged from 11 years to 17.7 years (mean of 13.8 years). The six patients with cataract used glucocorticoids from 10 to 84 months (mean of 45 months). Such patients received pulse therapy with methylprednisolone at the dosage of 30 mg/kg/day for three days, for a period ranging from 2 to 99 months. The cumulative glucocorticoid dose ranged from 35.5 g to 97.3 g. The age at which glucocorticoid use started varied from 7.9 years to 14.3 years (mean of 13.8 years).

The age of glaucoma onset varied from 10.9 years to 14.2 years (mean of 12.3 years). Patients with that complication used glucocorticoid from three to 53 months (mean of 21 months). The cumulative glucocorticoid dose ranged from 5 g to 40.5 g. One patient had irreversible unilateral vision loss secondary to corticosteroid-induced glaucoma.

The 24 patients with any ocular change were using glucocorticoid and hydroxychloroquine/chloroquine diphosphate on the occasion of the ocular change.

Patients with ocular changes received statistically higher and longer doses of glucocorticoid pulse therapy as compared with patients without ocular changes [1.5 (0.4–1.6) versus 1 (0.2–1.6) mg/kg, P = 0.003; 25.7 (2–99) versus 17.8 (1–114) months, P = 0.0001, respectively]. No statistic difference was observed in the other parameters evaluated (Table 1).

Eight (50%) out of the 16 patients with abnormal funduscopy had macula change associated with chloroquine use as follows: three were on hydroxychloroquine; two on chloroquine diphosphate; and three on chloroquine diphosphate and hydroxychloroquine afterwards. Those patients used their medications from one to five years (mean of 2.7 years). The mean age of ocular change onset related to hydroxychloroquine/chloroquine diphosphate use was 14.6 years. Three patients (37.5%) with macula change (two on chloroquine diphosphate and one on hydroxychloroquine) had to discontinue chloroquine.

Twelve (50%) of the 24 patients had a diagnosis of systemic arterial hypertension. Eight of them were on one or more antihypertensive drugs. Of the hypertensive patients, three (25%) had cotton wool spots and papilledema, changes consistent with arterial hypertension. Neither retinal vasculitis nor uveitis was described in any patient.

DISCUSSION

Most studies have described ocular changes related to SLE, and more rarely the consequent changes to medications or complications of the disease have been described. However, publications in pediatrics are scarce.[17] A study with 52 JSLE patients has reported a 34.6% frequency of ocular changes. Of those patients, 61.1% had JSLE for more than one year.[17]

According to reports in the literature, the prevalence of retinal changes resulting from SLE ranges from 3% to 50% of adult patients.[18,19] In our case series, the frequency of ocular changes was lower (20%).

A study has reported an approximate 70% frequency of keratoconjunctivitis sicca in patients with SLE.[20] We have not found that association on biomicroscopy to evaluate the ocular surface.

The ocular involvement has often been a late manifestation, because it has mostly resulted from complications of the treatment leading to cataract, glaucoma, and abnormal funduscopy.

We found ocular changes resulting exclusively from the use of glucocorticoid or chloroquine or consequent to systemic arterial hypertension. Biomicroscopy was routinely performed in all patients, but no uveitis was found. In the literature, uveitis has been reported as a rare finding.[13]

Glaucoma and cataract have been known to be complications of the treatment with systemic and local glucocorticoids,[9] which suggests that that medication may be involved in the genesis of the ocular change.

In severe cases, the ophthalmologic involvement may progress to legal blindness. Blindness resulting from previous uveitis has been reported in a patient with JSLE, and retinal vasculitis secondary to ocular infection by varicella zoster virus has been reported in another JSLE patient. The authors have concluded that the disease activity and infections may lead to those serious ocular sequelae.[21]

Chloroquine has been reported as capable of provoking retinal toxicity due to retina impregnation. Eight patients had abnormal funduscopy compatible with that adverse event. However, those abnormalities have been described when the drug is used for over five years, which did not happen with our patients, who had an earlier retinal change. No patient was receiving the drug at doses greater than those recommended. Regular ophthalmologic examinations every six months are required to early detect those alterations. Three patients on chloroquine had to discontinue the drug.

A study has reported that around 1%–2% of lupus patients had optic neuritis or ischemia, manifested as progressive visual loss and pale papilla.[19] Another study has found

5% of changes in the pigmented epithelium of retina.[22] We found no patient with those changes. Patients with SLE and high titers of anticardiolipin antibodies have a greater risk of developing occlusive ocular vascular disease.[18] Although we found seven patients positive for that antibody, none had thromboembolic disease.

In order to assess a greater population, multicenter studies are necessary to evaluate ocular changes in JSLE patients. Thus, risk factors or possible associations between those ocular changes and demographic data, disease activity and severity, cumulative damage, antiphospholipid antibodies, and treatment can be analyzed.

This study showed a high prevalence of abnormal funduscopy related mainly to the treatment of SLE. In conclusion, ophthalmologic examinations every six months are required even in asymptomatic SLE patients or those without associated diseases, aiming at the early diagnosis and intervention and at decreasing the disease-related ocular morbidity.

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