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ORIGINAL ARTICLE

Corneal vortex keratopathy in childhood-onset systemic lupus erythematosus (c-SLE)

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Abstract

Objective To describe the prevalence and risk factors associated with corneal vortex keratopathy in a childhood-onset systemic lupus erythematosus (c-SLE) cohort.

Material and methods Consecutive outpatients with c-SLE were evaluated by a pediatric ophthalmologist and pediatric rheumatologist in an outpatient clinic setting in an urban Children's Hospital. Demographic, clinical, laboratory, and disease characteristics were documented for each patient. Cumulative drug dosage, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology damage index (SLICC/ACR-DI) scores were calculated.

Results A total of 76 c-SLE patients (61 (80.26%) females; mean age = 17.9 (SD ± 3.07)) were included. Ophthalmologic abnormalities were observed in 36 (47.36%) patients of which 16 (21.10%) had corneal vortex keratopathy ($p = 0.03$). c-SLE patients with corneal vortex keratopathy were all female. We did not observe any additional clinical, laboratory, or treatment feature associated with corneal vortex keratopathy.

Discussion We observed a high prevalence of corneal vortex keratopathy in female c-SLE. We hypothesize that this finding may be an initial, dose-related toxicity due to antimalarial use. Follow-up studies are necessary to determine if these changes are an early predictor of retinal toxicity due to antimalarial in c-SLE.

Key Points • *Corneal vortex keratopathy was frequently observed in female patients with c-SLE on a chloroquine medication.*
• *Corneal vortex keratopathy may be an early marker of chloroquine retinopathy.*

Keywords Corneal vortex keratopathy · Ocular findings · Systemic lupus erythematosus

Introduction

Childhood-onset systemic lupus erythematosus (c-SLE) is a chronic, multisystemic, autoimmune condition with disease onset before the age of 18 [1–3]. Ophthalmologic manifestations can impact many components of the visual system during any time of the disease course and are associated with significant morbidity [4]. The prevalence varies across studies and is reported in up to 30% [1].

Ocular manifestations require careful evaluation in c-SLE since they may indicate the presence of disease activity or damage. Ocular disease activity can be secondary to immune complex deposition, antibody-related injury, vasculitis, or thrombosis [4]. The British Isles Lupus Assessment Group (BILAG) incorporated ophthalmic manifestations in their disease assessment score in 2004 to improve the activity index [5]. However, drug toxicity can also present with ocular manifestations [6]. In 1996, the Systemic Lupus International

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Collaborating Clinics (SLICC) damage index considered eye abnormalities (such as cataracts, retinal changes, or optic atrophy) as permanent damage [7]. Despite these efforts to include ocular complications, the descriptions of ophthalmologic changes in SLE are still scarce and do not accurately reflect the extent of involvement of the organ.

Most ocular structures can be affected by SLE, including the periorbital region, adjacent eye structures, uveal tract, and orbit and optic nerves. Keratoconjunctivitis sicca is the most frequent ophthalmic manifestation of c-SLE [8]. Corneal vortex keratopathy (or cornea verticillata) is characterized by a whorl-like pattern of grayish golden-brown deposits in the corneal epithelium [9]. It consists of intracellular deposits of inclusion bodies in the corneal epithelium. It has been described as a classic finding in patients with Fabry disease or as a side effect of a variety of medications including amiodarone as well as antimalarial and non-steroidal anti-inflammatories which are widely used by rheumatologists [10].

A routine annual ophthalmologic exam should be performed in c-SLE by an experienced ophthalmologist independent of symptomatology [6]. According to American Academy of Ophthalmology, chloroquine and hydroxychloroquine retinopathy screening and monitoring should include visual field testing and spectral domain optical coherence tomography (SD-OCT) [8].

Although antimalarial has been associated with corneal vortex keratopathy, this finding has not been reported in c-SLE thus far. In this study, we describe the prevalence and risk factors associated with corneal vortex keratopathy in our cohort.

Material and methods

Consecutive c-SLE patients [11], followed at the pediatric rheumatology outpatient clinic at Albert Sabin Children's Hospital, were invited to participate in this cross-sectional study from December 2014 to December 2017. This study was approved by the ethics committee of our institution. Informed consent was obtained from patients or their legal representative for children < 18 years.

Clinical evaluation

All patients were evaluated by a board-certified pediatric rheumatologist (LP).

A retrospective chart review was used to collect demographic and disease characteristics including date of birth, sex, and age at disease onset, clinical manifestations, and laboratory abnormalities, and current and past treatments. Cumulative doses of hydroxychloroquine and diphosphate chloroquine were calculated, summated, and reported as a total antimalarial dose.

SLEDAI was calculated for each patient at study visit [12] and disease was considered active for SLEDAI scores ≥ 3 [13]. SLICC/ACR-DI scores were also calculated for each patient at study visit and presence of damage was considered if scores ≥ 1 [7].

Ophthalmological evaluation

All patients underwent a complete ophthalmological examination by a board-certified pediatric ophthalmologist (PC, ICV). Positive findings were reviewed by a second board-certified ophthalmologist (PC, ICV). A third ophthalmologist was consulted in one case with discordant findings. Refractive errors were measured by a handheld autorefractor keratometer Retinomax K Plus 2. The best-corrected visual acuity of each eye was determined by Snellen letters and numbers chart, measured at a distance of 6 m for children above 6 years. Non-literate children's visual acuity was evaluated by the Snellen E and Snellen number chart at an appropriate distance. Anterior segment (cornea, iris, and lens crystalline) was evaluated by slit-lamp examination. Optic nerve, macula, and posterior pole vessels were analyzed with direct ophthalmoscopy. Intraocular pressure (IOP) was measured by applanation with Perkins tonometer method and was considered normal if ranged from 10 to 20 mmHg. A tear breakup time (TBUT) test was performed after placing a drop of fluorescein in the cul-de-sac in order to determine keratoconjunctivitis.

Statistics analysis

All statistical analyses were performed using SPSS 20.0 software package.

Results are shown in absolute number and percentage or in mean and standard deviation (SD). Chi-square or Fisher exact test was used to compare categorical variables.

Continuous variables were compared by ANOVA. A p value ≤ 0.05 was considered clinically significant.

Results

A total of 76 (61 (80.3%) females; mean age 17.9 (SD ± 3.07)) c-SLE patients were included. The clinical manifestations observed in c-SLE were as follows: arthritis (64.47%), malar rash (52.63%), photosensitivity (53.94%), leukopenia (44.73%), alopecia (42.10%), oral ulcer (39.47%), thrombocytopenia (31.57%), nephritis (27.63%), lymphopenia (23.68%), serositis (22.36%), neuropsychiatric lupus (NPSLE) manifestation (13.15%), hemolytic anemia (10.52%), and discoid lupus (2.63%).

Fifteen (19.73%) c-SLE had active disease at study evaluation. SLICC/ACR-DI scores ≥ 1 were identified in 18 (23.70%) c-SLE.

Ophthalmological abnormalities were observed in 36 (47.36%) c-SLE patients. The corneal vortex keratopathy was found in 16 (21.10%) patients with good inter-rater reliability. No cases of retinopathy were observed. Demographic characteristics, clinical features, immunoserologies, and treatments were compared in c-SLE patients with and without cornea verticillata and are shown in Table 1. Comparisons of additional ophthalmological abnormalities in c-SLE patients with and without corneal vortex keratopathy are summarized in Table 2.

Discussion

We observed corneal vortex keratopathy in 16 (21%) of our cohort. The presence of corneal vortex keratopathy was only identified in females ($p = 0.03$). We did not observe any other clinical, laboratorial, and treatment features and risk factors associated with the occurrence of the cornea verticillata. To our knowledge, no study has reported the occurrence of cornea verticillata in c-SLE so far.

Corneal vortex keratopathy is associated with systemic diseases, such as Fabry disease, multiple myeloma, corneal dystrophies, and side effects of systemic drugs [14]. Several drugs have been associated with the occurrence of corneal vortex

Table 1 Comparison of patient demographics, clinical features, immunoserologies, and treatment in c-SLE patients with and without corneal verticillata

Variables	c-SLE with cornea verticillata N = 16	c-SLE without cornea verticillata N = 60	*P* value
Female, N (%)	16 (100)	45 (75)	0.03
Age at disease onset			
(mean years ± SD)	13.56 ± 2.60	12.63 ± 2.9	0.27
Follow-up time (mean years ± SD)	5.06 ± 2.04	4.91 ± 2.19	0.93
Current age (mean years ± SD)	18.69 ± 3.07	17.68 ± 3.07	0.93
Clinical features			
Arthritis, N (%)	8 (50)	41 (68.33)	0.240
Nephritis, N (%)	5 (31.25)	16 (53.33)	0.758
Malar rash, N (%)	6 (37.5)	34 (56.66)	0.260
Photosensitivity, N (%)	7 (43.75)	29 (48.33)	0.785
Serositis, N (%)	3 (18.75)	14 (23.33)	1.000
NPSLE, N (%)	2 (12.5)	08 (13.33)	1.000
Immunoloserologies			
ANA antibodies, N (%)	16 (100)	58 (96.66)	1.000
ds DNA antibody, N (%)	7 (43.75)	24 (40)	0.783
Anti-Sm antibody, N (%)	6 (37.5)	9 (15)	0.073
Anti-RNP antibody, N (%)	2 (12.5)	6 (10)	0.672
Anti-Ssa/Ro antibody, N (%)	2 (12.5)	6 (10)	0.672
Anti-Ssb/La antibody, N (%)	2 (12.5)	4 (6.66)	0.593
Anticardiolipin antibody, N (%)	3 (18.75)	10 (16.66)	1.000
SLEDAI (mean ± SD)	2.50 ± 4,22	2.00 ± 2.83	0.123
SLICC ≥ 1	2 (12.5)	16 (26.66)	0.330
Treatment			
Prednisone current use, N (%)	14 (87.50)	40 (66.66)	0.129
Cumulative dose (mean ± SD)	17.50 ± 9.72	17.08 ± 8.00	0.67
Antimalarial current use, N (%)	16 (100)	60 (100)	1.000
Cumulative dose (mean ± SD)	425.7 (200.24)	294.42 (197.55)	0.667
Methotrexate, N (%)	2 (12.5)	10 (16.66)	1.000
Azathioprine, N (%)	3 (18.75)	15 (25.00)	0.748
Cyclosporine, N (%)	1 (6.25)	3 (5)	1.000
Cyclophosphamide, N (%)	5 (31.25)	16 (26.66)	0.733
Mycophenolate mofetil, N (%)	1 (6.25)	3 (5)	1.000

Table 2 Ophthalmological findings in c-SLE with and without cornea verticillata

Ophthalmological findings	c-SLE with cornea verticillata $N = 16$	c-SLE without cornea verticillata $N = 60$	P value
Fundoscopy abnormalities, N (%)	00	08 (13.33)	0.191
Visual acuity reduction, N (%)	03 (18.75)	22 (36.66)	0.237
Anterior chamber abnormalities, N (%)	02 (12.5)	02 (3.33)	0.193
Posterior subcapsular cataracts, N (%)	00	09 (15)	0.191
Keratitis, N (%)	00	02 (3.33)	1.000
Optic nerve abnormalities, N (%)	00	08 (13.33)	0.191
Crystalline abnormalities, N (%)	01 (6.25)	00	0.210
Antimalarial-induced retinopathy	00	00	–

keratopathy in the literature including antimalarial, amiodarone, non-steroidal anti-inflammatories, and chemotherapy [14]. Systemic drugs induce corneal epithelium changes through phospholipidosis, lysosomal sequestration, drug precipitation, or direct toxicity to the epithelial cells. Due to the normal migration of affected and non-affected cells from limbic stem cells to the center of the cornea, corneal changes are initially observed in the periphery, progressing to the center. This migration of cells along the cornea leads to the typical vortex pattern noted [14]. c-SLE patients in our cohort with corneal vortex keratopathy had a higher cumulative antimalarial dose. However, our study was not powered to show causality.

The presence of marked corneal vortex keratopathy has been described to be associated with retinopathy [14]. Retinal toxicity has been reported to occur in 7.5% of antimalarial users. Daily dose and duration of use of chloroquine and hydroxychloroquine determine the risk of ocular toxicity [15]. The absence of retinopathy in our patients can be due to the lower cumulative dose of diphosphate chloroquine (268.40 g) and hydroxychloroquine (401.09 g) in our cohort.

Current recommendations include optical coherence tomography (OCT) for screening in hydroxychloroquine retinopathy in SLE patients. OCT provides, in real time, qualitative (reflectivity and morphology) and quantitative (thickness, mapping, and volume) analyses of the retinal layers or under the retina, which may not be visible clinically [15, 16].

The guidelines recommend ophthalmologic evaluation before the use of hydroxychloroquine followed by an annual exam 5 years after initiating therapy [15].

We hypothesize that the finding of corneal vortex keratopathy may be initial toxicity due to antimalarial use. Follow-up studies are necessary to determine if these changes are indeed an early predictor of retinal toxicity due to antimalarial use in c-SLE and if more frequent ophthalmology exams and/or dose adjustments would be recommended as a result. For patients presenting only with drug-induced epithelial corneal changes, the treatment regimens are not altered because these findings are usually benign and asymptomatic, not resulting in decreased visual acuity [6].

In conclusion, we observed corneal vortex keratopathy in 21.1% of our c-SLE female cohort.

Follow-up studies are necessary to determine if these changes are early predictors of retinal toxicity due to antimalarial in c-SLE.

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Compliance with ethical standards

Disclosures None.

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