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Associated factors for steroid-induced ocular hypertension in children with systemic lupus erythematosus

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Abstract

This retrospective study investigated clinical factors associated with steroid-induced ocular hypertension in 49 pediatric systemic lupus erythematosus patients (mean age: 128.80 ± 34.6 months; 39 female and 10 male). All subjects underwent a 2-month follow-up with pretreatment assessment of age, sex, axial length, and clinical characteristics, including weight, systemic lupus erythematosus disease activity index (SLEDAI) scores, and erythrocyte sedimentation rate (ESR). Post-treatment variables were collected at the end of the 2-month follow-up, included the development of central obesity, elevated low-density lipoprotein levels, administration of pulsed intravenous steroid therapy, and cumulative methylprednisolone dosage. Forty-nine eyes of 49 patients were enrolled. Sixteen (32%) patients were diagnosed with steroid-induced ocular hypertension. One random eye was enrolled for each subject to avoid statistical bias. Steroid-induced ocular hypertension occurred from 3 d to 3 weeks following systemic steroid administration. No statistically significant differences were observed in pretreatment demographics, clinical characteristics, cumulative methylprednisolone exposure, low-density lipoprotein elevation, or pulsed intravenous therapy between patients with and without ocular hypertension. Notably, steroid-induced central obesity is associated with ocular hypertension (OR = 7.909 [95% CI: 1.382–45.256]) while no one had central obesity before steroid administration. This association persisted after multivariable adjustment for age, sex, weight, axial length, and SLEDAI scores (OR = 11.632 [95% CI: 1.131–119.633]). These findings suggest that pediatric patients who develop central obesity within the first 2 months of systemic steroid administration should undergo close intraocular pressure monitoring to facilitate early detection and prevention of steroid-induced glaucoma.

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Introduction

Steroids are one of the most common anti-inflammatory drugs used worldwide because of their profound immunomodulatory actions[1]. Unfortunately, their therapeutic benefits are often limited by adverse side effects. One of the most significant ocular side effects is steroid-induced ocular hypertension[2], which refers to an elevation in intraocular pressure (IOP) resulting from topical or systemic steroid administration. Steroid responsiveness varies among individuals—approximately 30%–40% of the general population may experience IOP elevation with steroid use, though not all develop steroid-induced ocular hypertension or glaucoma. Individuals who exhibit IOP elevation in response to steroids are referred to as 'steroid responders'. Armaly, and Armaly & Becker, who first reported steroid-induced ocular hypertension in 1965[3,4], defined steroid responders as those with an IOP increase of at least 5 mmHg following steroid therapy. If this elevation is not properly managed, it can lead to optic nerve damage and irreversible vision loss, ultimately progressing to steroid-induced glaucoma (SIG). Therefore, early detection and management of steroid-induced ocular hypertension after steroid administration are essential. However, since the condition is often asymptomatic[5], the early detection of steroid-induced ocular hypertension relies on regular IOP monitoring following steroid use. Comprehensive monitoring of all patients receiving steroids however demands significant resources, including healthcare personnel, financial costs, and time.

An affordable approach is to closely monitor patients at high risk. Although researchers have identified several risk factors for steroid-induced ocular hypertension and glaucoma[6], including a history of primary open-angle glaucoma (POAG)[7,8], high myopia[9], angle-recession glaucoma[10], connective tissue disease[11], and diabetes mellitus[12], a substantial number of patients without these known associated factors still develop the condition. Therefore, identifying associated factors of steroid responders is essential to help narrow the scope of screening—particularly in children, who may experience earlier onset and more rapid progression of IOP elevation and glaucomatous damage compared to adults[13–16]. In this study, clinical data from pediatric patients receiving systemic steroid therapy was reviewed and analyzed to identify associated factors associated with steroid-induced ocular hypertension. The goal was to determine predictors of steroid responders who warrant increased attention for IOP monitoring following steroid administration.

Methods

This retrospective study was conducted with adherence to the tenets of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Local ethical approval was obtained from the Ethics Committee of Sun Yat-sen Memorial Hospital at Sun Yat-sen University, Guangzhou, China (Approval No. SYSEC-KY-KS-2020-158). The medical charts of patients with systemic lupus erythematosus (SLE) within Sun Yat-sen Memorial Hospital from January 1, 2017, to December 31, 2019, were reviewed. The inclusion criteria were as follows: individuals (1) aged 5 to 18 years; (2) with a history of steroid treatment; and (3) who were followed up for 2 months to ensure that late-onset steroid-induced ocular hypertension was not missed, which, as previously reported[17], commonly occurs in 3 to 6 weeks. The exclusion criteria were as follows: individuals, (1) with no detailed history of steroid usage; (2) no detailed history of ophthalmology; and (3) a history of ocular disease or previous intraocular surgery.

One random eye was enrolled for each subject to avoid statistical bias. Steroid-induced ocular hypertension was defined as IOP elevation > 5 mmHg following steroid therapy from baseline and IOP above 24 mmHg. IOP was measured by non-contact tonometry (NCT) in the morning. The IOP were measured every week in the first months and twice a week in the second month. The patients' demographic information, clinical characteristics, eye parameters (axial length (AL) and corneal thickness), side effects from steroids (the development of central obesity and elevation of low-density lipoprotein (LDL) levels), and the central obesity and LDL levels were assessed at 8 weeks after the first steroid therapy in the regular follow-up visits. Administration of pulsed intravenous steroid therapy and cumulative methylprednisolone dosage within the initial 2 months were collected and further analyzed. All ALs were measured by partial coherence interferometry (IOLMaster, Software V5.4 and later, Carl Zeiss Meditec, Inc., Dublin, USA). Center corneal thicknesses were measured by A-scan. The age-specific and sex-specific waist-to-height ratio (WHtR) cutoffs were used to define central obesity for Chinese children[18,19]. The WHtR is calculated as the waist circumference (cm) divided by height (cm), expressed as: WHtR = Waist circumference (cm) ÷ Height (cm). The patient demographics (age, sex, and weight), and clinical data were used to evaluate the activity of SLE (systemic lupus erythematosus disease activity index [SLEDAI] scores and erythrocyte sedimentation rate [ESR]).

Statistical analysis

Quantitative variables were computed as the mean ± standard deviation (SD). The differences in characteristics and clinical factors between steroid responders and nonsteroid responders were assessed using the Wilcoxon signed-rank test, independent *t*-test, or Chi-square test. The logistic regression analysis was employed to adjust for the demographics and clinical characteristics. *p*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using R software (R version 4.4.3).

Results

This study enrolled 49 eyes from 49 subjects. All subjects were steroid-sensitive for SLE. Thirty-two percent of the patients were diagnosed with steroid-induced ocular hypertension (16 of 49 patients), which is similar to the values reported in previous studies[20]. All steroid responders were diagnosed with steroid-induced ocular hypertension in both eyes. Steroid-induced ocular hypertension occurred from 3 d to 3 weeks following systemic steroid administration. Table 1 summarizes the baseline characteristics of the subjects, including their demographics, AL, and center corneal thickness. Whether baseline characteristics were different between the two groups before treatment were further analyzed, the results reveal that there were no statistically significant differences between the steroid responders and nonresponders groups in terms of sex, age, weight, SLEDAI scores, ESR, AL and center corneal thickness before treatment, and none have central obesity before steroid administration. All patients in this study had no high myopia, and the AL ranged from 21.6 to 25.55 mm.

The results suggested that the steroid-induced central obesity had statistically significant differences between the steroid responder and non-responders groups, with an OR = 7.909 (95% CI: 1.382–45.256), while there were no statistically significant differences in methylprednisolone accumulation, pulsed intravenous therapy, or LDL elevation after treatment between the steroid responders and nonresponders. The results were summarized in Table 2. Additionally, the subgroups of age (< 144 months, and > 144 months) and of sex (female and male) were also analyzed respectively, but no statistically significant association was found except the steroid-induced central obesity in the female subgroup (Table 3). Multivariate Logistic regression analysis was conducted to eliminate collinearity. The results revealed that after adjusting for sex, age, AL, SLEDAI score and weight pre-treatment, the OR of steroid-induced central obesity was 11.632 (95% CI: 1.131–119.633) (Table 4), this model Hosmer and Lemeshow Test *p*-value is 0.322, and this model accounted for 76.5% of the global variations on steroid-induced ocular hypertension, the sensitivity of this model is 56.25%.

Discussion

This study highlights that steroid-induced central obesity is associated with steroid-induced ocular hypertension. One-third of the children who developed ocular hypertension following steroid treatment exhibited central obesity, and after adjusting for age, sex, and weight, the development of central obesity within the first 2 months of steroid therapy was found to be significantly

Table 1. Baseline characteristics of subjects.

Characteristic	Steroid responders (n = 16)	Non-responders (n = 33)	Total (n = 49)	*p* value
Demographics				
Sex, female, n (%)	12 (75%)	27 (82%)	39 (80%)	0.29*
Age (months)	131.41 ± 30.36	127.41 ± 37.04	128.80 ± 34.6	0.70
Clinical characteristics (before treatment)				
Weight (pre-treatment)	30.88 ± 10.28	30.65 ± 10.45	30.74 ± 10.26	0.95
SLEDAI scores	13.18 ± 9.11	16.22 ± 9.59	15.16 ± 9.44	0.29*
ESR	49.50 ± 35.15	59.83 ± 35.99	56.24 ± 35.66	0.36*
Axial length	23.61 ± 0.97	23.87 ± 0.96	23.71 ± 0.96	0.41*
Center corneal thickness	547.63 ± 40.677	547.62 ± 33.71	546.32 ± 37.90	0.88

* $p \leq 0.05$ were considered statistically significant.

Table 2. Analysis of associated factors for steroid-induced intraocular hypertension.

	Steroid responders (n = 16)	Non-responders (n = 33)	Total (n = 49)	*p* value	OR	95% CI
Pulsed intravenous therapy, n (%)	11 (69%)	25 (76%)	36 (73%)	0.28	0.44	0.11–1.84
Steroid-induced central obesity, n (%)	6 (38%)	2 (6%)	8 (16%)	0.02*	7.909	1.38–45.26
Subjects with low-density lipoprotein elevation, n (%)	8 (50%)	14 (42%)	22 (45%)	1	1.08	0.33–3.54
Methylprednisolone accumulation, mean ± SD (mg)	2,585.38 ± 2,171.97	2,796.52 ± 1,729.38	2,720.28 ± 2,000.30	0.13	1.67	0.56–2.34

* $p \leq 0.05$ were considered statistically significant.

Table 3. Analysis of associated factors for steroid-induced intraocular hypertension in subgroups.

	p value			
	Sex subgroups		Age subgroups	
	Male	Female	≤ 144 months	> 144 months
Pulsed intravenous therapy	0.50	0.10	0.1	1.0
Steroid-induced central obesity	0.86	0.01*	0.19	1.0
Low-density lipoprotein elevation	0.53	0.66	0.71	0.88
Methylprednisolone accumulation	0.23	0.12	0.21	0.56

* $p \leq 0.05$ were considered statistically significant.

Table 4. The logistic regression analysis of associated factor for steroid-induced intraocular hypertension.

Variable	B	SE	Wald	df	*p* value	OR	95% CI for OR
Sex	0.78	0.97	0.64	1	0.42	2.18	0.32–14.65
Age	−0.01	0.13	0.19	1	0.89	0.10	0.97–1.02
Weight (pre-treatment)	−0.11	0.05	0.55	1	0.81	0.99	0.91–1.08
SLEDAI score	−0.04	0.06	0.53	1	0.47	0.96	0.86–1.07
Axial length	0.47	0.47	0.97	1	0.33	1.59	0.63–4.02
Steroid-induced central obesity	2.45	1.19	4.26	1	0.04*	11.63	1.13–119.63
Interaction effects	0	0	2.64	1.00	0.11	1.00	1.00–1.00

* $p \leq 0.05$ were considered statistically significant.

associated with steroid-induced ocular hypertension. Since Armaly first reported steroid-induced IOP elevation in 1965[3], this side effect has been extensively studied to prevent vision loss resulting from SIG. Previous studies[8–12,21] have identified several risk factors for steroid responsiveness, including a history of POAG, angle-recession glaucoma, high myopia, connective tissue disease, a glucocorticoid dosage exceeding 7.5 mg/d, and diabetes mellitus.

Compared to adults, IOP elevation and the resulting glaucomatous damage in children can be more severe. In a retrospective study[22], Gupta et al. analyzed 1,259 pediatric glaucoma patients, 59 of whom were diagnosed with SIG. Of these patients, 51 (87%) had glaucoma induced by topical steroids for vernal keratoconjunctivitis, and the rest had received systemic steroids. Patients had irreversible vision loss caused by severe optic neuropathy at presentation: 14 children (23.7%) had low vision, 22 (37.3%) were bilaterally blind, and 16 (27%) were unilaterally blind. In another retrospective study[23], Senthil et al. reported similar findings regarding the prevalence of blindness associated with SIG in young patients with vernal keratoconjunctivitis. Among 4,062 subjects, 91 patients (157 eyes) were diagnosed with SIG. Of these eyes, 123 (78.3%) exhibited glaucomatous optic disk damage, while the remaining 34 (21.6%) had ocular hypertension. The disease was often advanced at presentation: 29 patients (36.9%) were bilaterally blind, and 10 (6.4%) were unilaterally blind.

Although steroid-induced ocular hypertension or glaucoma is more commonly associated with topical administration, the risk following systemic steroid use may be more easily overlooked, as patients receiving systemic steroids are typically managed by non-ophthalmologists. Only a few studies have specifically investigated risk factors for steroid-induced ocular hypertension resulting from systemic administration. In a retrospective study by Takano et al. involving 78 children under 20 years of age who received systemic steroids, 30 patients (38.5%) were identified as steroid responders, a proportion comparable to that in the present study (16 patients, 32%)[24]. Their findings suggested that high-dose steroid administration, male sex, and younger age were associated risk factors. However, in the present study, age, sex, and cumulative methylprednisolone dosage were not statistically significant. These discrepancies may be attributed to differences in ethnicity, underlying disease, or age distribution between cohorts.

Similarly, Lee et al.[20] retrospectively analyzed the medical records of 238 Korean children with chronic glomerulonephritis who underwent systemic corticosteroid therapy. Ocular hypertension was observed in 92 patients (39%). Interestingly, no correlation was found between ocular hypertension and corticosteroid treatment duration, total dose, weight-adjusted dose, daily dose, or the frequency of intravenous methylprednisolone pulse therapy.

In the present study, instead of BMI, central obesity—assessed by WHtR—was used to evaluate steroid-induced obesity[25]. In another study, Krag et al. analyzed risk factors for steroid-induced ocular hypertension in 90 children with acute lymphoblastic leukemia and found that body mass index (BMI), and dexamethasone therapy were significant risk factors[26]. The present results also support that central obesity is significantly associated with steroid-induced ocular hypertension.

There are several limitations in this study. First, the study population did not include individuals with high myopia, which has been reported in previous studies as a potential risk factor for steroid-induced ocular hypertension or glaucoma. Another limitation is the relatively short follow-up duration. Although all cases of steroid-induced ocular hypertension in this 2-month cohort occurred within 3 d to 3 weeks of initiating systemic steroid therapy—and previous studies have shown that IOP typically normalizes once steroid treatment is discontinued[6,26]—most patients with SLE require multiple courses of intravenous methylprednisolone pulse therapy along with long-term maintenance glucocorticoid treatment. Therefore, longer follow-up periods are necessary in future studies to fully assess the risk and trajectory of steroid-induced ocular hypertension in this population.

In this study, neither the total corticosteroid dose nor the administration of intravenous methylprednisolone pulse therapy was associated with steroid-induced ocular hypertension, consistent with findings from previous research. Additionally, the results showed no correlation between steroid-induced ocular hypertension and either the severity of SLE, or the post-treatment elevation in LDL levels. While previous studies have suggested that high myopia may be an associated factor for steroid-induced ocular hypertension, the present findings indicated that among patients without high myopia, AL was not associated with steroid-induced ocular hypertension or central corneal thickness. Notably, the development of central obesity following treatment was significantly associated with steroid-induced ocular hypertension, suggesting that central obesity is associated with steroid sensitivity in this context. This may be explained by the fact that both central obesity and steroid-induced ocular hypertension are regulated by glucocorticoid receptors[27–29]. However, the precise underlying mechanisms remain unclear and warrant further investigation.

Conclusion

This study suggested that steroid-induced central obesity is associated with steroid-induced ocular hypertension. The IOP of patients who develop central obesity within the first 2 months of systemic steroid administration should undergo close IOP monitoring to facilitate early detection and prevention of SIG.

Ethical statements

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital at Sun Yat-sen University (Approval No. SYSEC-KY-KS-2020-158). All participants or their legal representatives reviewed and signed written informed consent forms.

Author contributions

The authors confirm their contributions to the paper as follows: study conception and design: Zhang B, Zhou C, Lai Y, Zhang C, Zhang Y; material preparation, data collection, and analysis: Zhang B, Zhou C, Lai Y, Zhang C, Zhang Y; first draft of the manuscript: Zhang Y; comments on previous version of the manuscript: Zhang B, Zhou C, Lai Y, Zhang C, Zhang Y. All authors reviewed the results and approved the final version of the manuscript.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of interest

The authors declare that they have no conflict of interest.

Dates

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