The Occurrence Timeline of Steroid-induced Ocular Hypertension and Cataract in Children With Systemic Autoimmune Diseases

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Abstract

Purpose Steroid-induced ocular hypertension (SIOH) and cataract can result in visual loss. This study evaluated the timetable of SIOH and steroid-induced posterior subcapsular cataract (SI-PSC) occurrences in children with systemic autoimmune diseases (SAD) undergoing long-term systemic corticosteroid treatment.

Methods Thirty-seven children with SAD treated with long-term oral corticosteroids were enrolled in this study. Intraocular pressure (IOP), SI-PSC occurrences, visual field and peripapillary retinal nerve fibre layer (pRNFL) thicknesses were recorded every 3 months for at least 6 months.

Results Of the 37 children, with average age 11.0 ± 2.9 years, 22 patients (59.5%) had SIOH, 2 progressed as glaucoma at the 18-month and 3-year follow-up respectively and 12 (32.4%) patients had SI-PSC. Among patients with SIOH, 45.5% (10/22) of them had SI-PSC occurrences and among patients with normal IOP, 13.3% (2/15) of them had SI-PSC. Seventeen patients participated in a longitudinal study with a follow-up period of at least 18 months. The incidence of SIOH started at 1 month (52%, 9/17) and gradually increased to its peak value (70.6%, 12/17) at 6 months, then decreased to 35.3% (6/17). SI-PSC onset started at 6 months (17.6%, 3/17), and its occurrence increased to 35.3% (6/17) at 12 months and reached to 41.2% (7/17) at 18 months. The pRNFL was thicker in the children with SIOH than the healthy controls ($p = 0.01$).

Conclusion SIOH and SI-PSC are common coexistent complications in children with long-term corticosteroids treatment and the occurrence time is during the first month and 6 months, respectively. Patients with SIOH have a higher probability of cataract.

Background

Corticosteroids have potent anti-inflammatory and immunosuppressive activities and are usually chosen for treating autoimmune diseases. The adverse events of long-term oral corticosteroids therapy are still a major concern in the management of systemic autoimmune conditions. Steroid-induced ocular hypertension (SIOH) and posterior subcapsular cataract (SI-PSC) are the most common ocular issues, especially in paediatric patients[1].

SIOH is defined as the elevation of intraocular pressure (IOP) due to long-term corticosteroid usage. If long-term ocular hypertension remains unrecognised, it will lead to progressive damage to the optic nerve and induce irreversible visual loss and defect of visual field, which is known as steroid-induced glaucoma. Though patients of any age can get steroid-induced IOP elevation, IOP elevation and visual field damage can be more severe and rapid in children than in adults [2] [3] [4]. Young patients have longer remaining life spans than adults. The damage to vision and visual field will have a greater adverse influence on their daily life and cause a significant health burden for society. Thus, more attention should be paid to IOP in children undergoing long-term systemic steroid treatment. The precise mechanism for SIOH is not clear. Study found that steroid-induced changes may occur at the subendothelial region at the inner wall of the schlemm canal, which will cause fibrillary material deposited, then decreased trabecular meshwork outflow[5].

SI-PSC is a subtype of cataracts, and long-term corticosteroids treatment is an established risk factor for its formation [6]. In 1960, Black was the first to report that patients with rheumatoid arthritis who had been treated with long-term general corticosteroid had SI-PSC [7]. The dosage and duration of steroid treatment have been reported to be associated with the degree of PSC [7] [8]. The characteristics of steroid-induced cataracts include PSC, which mostly affects both eyes and progresses slowly. Most cataracts do not have an impact on vision; however, those with impaired vision due to cataracts will undergo cataract surgery. The etiology of steroid cataract have been found that glucocorticoids may induce changes to the transcription of genes in lens epithelial cells which are related to the cellular processes. It is account for the development of PSC[6]. Children are in a critical period of vision development; a severe cataract impedes the vision development of young patients, resulting in the formation of amblyopia. In children, cataract surgery is also more challenging and there are more complications in this patient group than in adults [9]. Consequently, when children with autoimmune diseases undergo long-term systemic steroid treatment, it is necessary to perform a slit-lamp examination for cataract at every follow-up.

Although both SIOH and SI-PSC are common ocular complications in patients with long-term systemic steroid treatment, there are limited data on the relationship of hypertension and cataracts in children who use oral corticosteroids for a long period of time. Thus, the present study aimed to observe the prevalence and onset time of SIOH and SI-PSC and the timelines of their occurrences and evolution in children undergoing long-term systemic steroid therapy.

Subjects And Methods

The prospective and longitudinal study was conducted at the Department of Ophthalmology in Beijing Children's Hospital, Capital Medical University in China from November 2017 to February 2019, after receiving approval from the institutional ethics committee. The study was conducted in adherence with the tenets of the Helsinki Declaration. Thirty-seven consecutive children with autoimmune diseases diagnosed by senior doctors of the Department of Rheumatology and Immunology in Beijing Children's Hospital, were enrolled. Healthy children with normal best corrected visual acuity (BCVA) and normal IOP (11–21 mmHg) who visited our hospital for physical examinations were enrolled as healthy controls (HCs) and their age and gender were matched to the study group. Written informed consent was obtained from the parents or guardians of each of the study's subjects.

All the patients had undergone standard long-term systemic steroid treatment in which methylprednisolone was administered intravenously 10–30 mg/kg/d for 3 days, followed by an oral steroid at a dose of 1–2 mg/kg/d for 2 to 4 weeks, and tapered by 5 mg/w until the minimal required dose (5 mg) to prevent remission. Patients with a family history of glaucoma and ocular diseases or ocular surgeries, with a follow-up time less than 6 months and who did not regularly use steroids were excluded from the study. Among the 37 cases with at least 6 months of follow-up, 17 patients who completed more than 18 months of follow-up were enrolled in the longitudinal study group.

Ophthalmologic examinations

Each patient underwent a BCVA test with the Snellen Chart, anterior and posterior segment evaluation by slit-lamp microscopy and indirect ophthalmoscopy. Len PSC was evaluated by slit-lamp microscopy. Visual field acuity was detected by Octopus automated perimetry (OCTOPUS 900, EyeSuite Static perimetry, V3.6.1, HAAG-STREIT, Switzerland) for the patients older than 5 years of age.

IOP measurement and cataract evaluation

IOP was measured by an iCare rebound tonometer (Icare Finland, Oy) 6 times and the average values were recorded to avoid variations. Ocular hypertension was defined as IOP > 21 mmHg or an IOP increase of > 6 mmHg in comparison to IOP before steroid treatment. Patients with IOP > 21 mmHg were given medication to control IOP. It usually begins with a beta-blocker, followed by carbonic anhydrase inhibitors and topical prostaglandins to control the pressure. IOP is closely monitored every week until it is normal. In our study, IOP was measured in all the patients before steroid treatment and monitored once a week in the first month and 2 weeks thereafter. The IOP values and the number of anti-glaucoma eye drops that were administered were recorded every 3 months and an index was used to evaluate the degree of IOP for at least 6 months. The criteria for diagnosing determination of PSC were guided by the procedure reported by Crews [10]. Every 3 months, the patients underwent a lens examination by slit-lamp microscope to determine the occurrence of PSC.

Optical coherence tomography (OCT) examinations

The results of visual field acuity for children are less reliable due to poor patient cooperation. Changes in the peripapillary retinal nerve fibre layer (pRNFL) thickness were detected using the Heidelberg Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) machine according to the standard protocols to monitor glaucomatous onset and progression. All the OCT examinations were performed by the same, experienced ophthalmologist.

Statistical analyses

Statistical analysis was performed using a statistical software package (SPSS, version 16.0; IBM Corp, Armonk, NY, USA). Frequency and descriptive statistics were used for the data analysis. Demographic and clinical characteristics, including age and pRNFL, were compared using independent sample t-tests. Sex and the cataracts in patients with SIOH hypertension and normal IOP were compared using the Chi-squared test, and the variables were tested for normality at the same time. The results are presented as means $\pm$ standard deviation (SD). A p value < 0.05 was considered statistically significant.

Results

Demographic and clinical features

A total of 56 children were enrolled in this study. Nineteen patients were excluded, including 9 patients who did not use steroids regularly, 7 patients that had used steroids for less than 6 months, 2 patients with a history of eye trauma and 1 patient with optic disc swelling (Fig. 1). Thus, a total of 37 patients were included; of these, 12 were boys and 25 were girls. Their ages ranged from 5 to 16 years (mean $\pm$ SD: 11.0 $\pm$ 2.9 years). Seventeen patients had a follow-up time of more than 18 months and were assigned to the longitudinal study group, with ages ranging from 7 to 16 years (mean $\pm$ SD: 11.3 $\pm$ 2.6 years). They mainly suffered from systemic lupus erythematosus, allergic purpura, dermatomyositis and rheumatoid arthritis. There were 22 patients (59.5%) with SIOH and 12 patients (32.4%) with SI-PSC. All but one of the ocular hypertension patients had binocular cataract. Two of these patients had visual field damage and were diagnosed with steroid-induced glaucoma. One girl had ocular hypertension in one eye and visual field damage after undergoing steroid treatment for 3 years. The cataracts were bilateral in all but one of the patients. All the demographic and clinical features are listed in Table 1.

IOP alterations and cataract occurrences with time

The incidence of IOP hypertension and cataracts in all the study patients are presented in Fig. 2. In the patients with SIOH, 10 patients got cataracts (45.5%) and 12 did not. In the patients with normal IOP, 2 got cataracts (13.3%), 13 did not. The incidence of cataract was much higher in the patients with an elevated IOP than in the patients with normal IOP; however, the difference was not statistically significant ($p = 0.07$). One special case was about a 16-year-old girl who was diagnosed with systemic lupus erythematosus (SLE) and treated with oral steroids for 3 years. When she came to the hospital for the pain and low vision of the left eye, IOP showed 18 mmHg of the right eye and 57 mmHg of the left eye. the C/D of the right eye was 0.2, and the C/D of the left eye was 0.9. OCT examination showed RNFL was severely thinner of the left eye. She was diagnosed with one eye glaucoma and the other eye was normal (Fig. 3).

There were 17 patients whose regular follow-up data were collected every 3 months for more than 1.5 years. The basic data are presented in Table 1; the total anti-glaucoma eyedrops and SI-PSC situations are presented in Table 2. The timeline of the number of anti-glaucoma eyedrops and cataract occurrence are shown in Fig. 4; 9 (52.9%) of the patients with elevated IOP appeared within the first month after steroid treatment. Its incidence gradually increased to the peak value (70.6%, 12/17) in 6 months, then it decreased to 35.3% (6/17) in 18 months. The degree of ocular hypertension was reflected by the number of anti-glaucoma medicines administered, beginning with 21 counts for 1 month, increasing to 22 counts at 3 months and reaching its peak of 24 counts at 6 months. It then gradually decreased to 13 counts at 18 months.

The earliest occurrence of SI-PSC was 6 months after steroid treatment and the onset time for most of the cataracts (6/7) occurred from 6 months to 1.5 years. All but one of the patients who acquired SI-PSC got SIOH. None of the 17 patients had progressed glaucoma or suffered visual field and optic nerve damage.

Optic nerve alterations detected by OCT

We compared the pRNFL between the patients with SIOH and the HCs (Table 3). Seven regions were analysed and compared, including RNFL-G T TS TI N NS and NI. There were no significant differences in the pRNFL thickness ($p \geq 0.05$) between the two groups except for the RNFL-NI region (control group 102.0 $\pm$ 19.8 μ m, study group 109.8 $\pm$ 22.4, $p = 0.01$). We compared the pRNFL between the eyes with hypertension and the HC group and found that the pRNFL was

thicker in the G, TS, N, NI regions of the eyes with hypertension ($p = 0.01, 0.03, 0.02, 0.00$, respectively). No significant difference was found in the pRNFL between the patients with normal IOP and the HCs.

Discussion

We performed a detail analysis of children with systemic autoimmune diseases who had undergone treatment with oral steroids for more than 6 months. We found that ocular hypertension and cataracts are the most common ocular complications and the patients with ocular hypertension had a higher percentage of cataracts than the patients with normal IOP. We also found that the pRNFL was thicker in patients with SIOH than the HC group.

In this study, 59.5% of the patients got IOP hypertension. Previous studies have reported that children are considered to be particularly susceptible to developing SIOH [11] [12]. Kwok et al. found that ocular hypertension occurs more frequently, more severely and more rapidly in children than in adults using topical dexamethasone [13]. Systemic steroids can also be considered to cause significant, but asymptomatic, ocular hypertension in paediatric patients [14] [15]. Grossman [16] reported on 1133 children treated with a systemic steroid and found that 37% of the patients developed elevated IOP. Because of oral steroids and topical steroids elevate IOP in different ways, Savleen Kaur reported that the elevation of IOP was lower and was controlled with fewer doses of drugs in patients receiving oral steroids in comparison to patients using topical steroids [17]. A majority of studies have reported that IOP increases 3–6 weeks after the beginning of topical steroid use, and some IOP hypertension can be found as early as the first or second week [2] [18] [19] [20]. Prasad found that increased IOP occurred in 61% of patients in the first month and in 87.9% of patients in the first 6 months of systemic steroid treatment [21].

In our study, the earliest response happened during the first week, and most of the patients got ocular hypertension during the first year. In half of the patients with ocular hypertension, elevated IOP appeared within the first 6 months. The number of new patients with ocular hypertension decreased gradually with the extension of the duration of steroid use and the number of anti-glaucoma medications decreased. Chen reported that the IOP can return to baseline once the use of corticosteroids is terminated [22]. We consider that, as the steroid dose is decreased, the IOP can gradually return to normal and fewer number of patients will have IOP hypertension. The pathophysiology of IOP hypertension is such that the steroids act on the glucocorticoid receptors on the trabecular meshwork, induce decreased cellularity of the trabecular meshwork and increase extracellular matrix deposition; this blocks the outflow of aqueous humour and increases IOP [23].

There were 32.4% of the patients got PSC. Kaye [24] and Hayasaka [25] reported that 30% and 33.3% of the patients in their study got PSC after long-term oral prednisone therapy. The prevalence of cataracts was similar to that reports. Some studies have claimed that the incidence of PSC was influenced by the medication dose and the duration of the cataracts; a higher total steroid dose and a longer time could induce a higher incidence of cataracts [25][26]. In our study, the earliest onset time of cataracts was 6 months after steroid treatment and most of the cataracts happened over the course of 1 to 1.5 years. It demonstrates that the occurrence of cataracts is dependent on the duration of the steroid therapy; thus, the longer the treatment time, the greater the possibility of developing cataracts. Loredó et al. reported that two patients got cataracts within the first year of steroid treatment [27]. Bachmann found that two children with nephrotic syndrome (NS) developed PSC after 7 and 8 months of steroid treatment [28]. The mechanism of SI-PSC is unknown, and there is no effective treatment except for removal of the cataracts if vision is significantly decreased [6] [29]. In our study, none of the patients' vision was affected by cataracts, and Urban et al. reported that visual impairment was rare in the PSC induced by corticosteroid use [30]. However, if cataract seriously affects the patient's vision, surgery is the best choice.

In our study, the incidence of cataracts was higher in the patients with IOP hypertension than in the patients with normal IOP (45.5% vs 13.3%, $p = 0.07$). Moreover, all but one of the patients with cataracts got IOP hypertension during the follow-up period. Is there a relationship between steroid-induced IOP hypertension and cataracts? The association between SIOH and SI-PSC has not been reported. A study on 336 patients found that 19 had cataracts caused by long-term oral corticosteroid therapy and 1 had glaucoma attributed to systemic steroid therapy [31]. The patient with glaucoma also had cataracts. The pathogenesis of glucocorticoid-induced cataract is complex. While many theories have been put forward [33], the formation process of PSC cannot be fully explained. TGF- β had been proven to be related to the development of posterior capsule transition [32]. Fini et al. stated that excessive TGF- β signalling could lead to ocular hypertension in mouse models [33]. TGF- β signalling for PSC and ocular hypertension is a subject for further research.

One patient in our study got glaucoma after using a low-dose oral steroid for 3 years. This demonstrates that, although most of the patients had normal ocular hypertension after their steroid dose is decreased, some patients can still get glaucoma. Thus, IOP should be monitored if a patient is still using steroids.

We found that the pRNFL was thicker in the group of patients with IOP hypertension than in the HC group. This is an interesting finding. We speculate that the observed increase in pRNFL thickness in our patients may reflect an early transient change caused by IOP hypertension. To the best of our knowledge, no previous study has reported a similar result. Aksoy et al. found that there were no statistically significant differences between the ocular hypertension group and the control group [34]. A longer observation time and more subjects are needed to study this further.

This study had several limitations. First, there may have been a bias in choosing the patients because most of our patients were from the Department of Rheumatology and Immunology. Second, we could not obtain visual field data for all the patients because visual field acuity results for children are less reliable due to poor patient cooperation and because the follow-up time was not long enough. Third, the sample size is small. Fourth, the follow-up time is too short.

In conclusion, ocular hypertension and cataracts are the most common complications in children that have long-term oral steroid use. The highest incidence of ocular hypertension occurs in the first 6 months of steroid use and the highest incidence of cataracts occurs after the first year. Regular IOP and slit-lamp examinations should be done in children with long-term steroid use. The incidence of cataract is higher in patients with IOP hypertension than in patients with normal IOP.

Declarations

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The authors have no financial or proprietary interests in any material discussed in this article.

Availability of data and material:

data transparency

Code availability:

not applicable

Authors' contributions:

Honggai Yan: Collected and performed the data analyses; wrote the manuscript.

Xiaohua Tan, Jifeng Yu, Tianwei Liang: contributed significantly to analysis and manuscript preparation.

Wei Shi, Li Li, Chunxia Peng: contributed to the conception of the study and helped perform the analysis with constructive discussions.

Ethics approval:

appropriate approvals have been approved.

Consent to participate:

appropriate statements have been signed

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Tables

Table 1
Demographic and clinical features for subjects included.

Variables	Total patients	Longitudinal patients	HCs	P value
Subjects	37	17	68	
Age(mean $\pm$ SD), y Range	11.0 $\pm$ 2.9 (5–16)	11.3 $\pm$ 2.6 (7–16)	10.4 $\pm$ 2.2 (6–16)	0.25
Gender(F/M)	12/25	8/9	29/39	0.30
Autoimmunity disorders n (%)			-	-
SLE	18(48.6%)	8(47.1%)		
Dermatomyositis	9(24.35)	7(41.2%)		
RA	4(10.8%)	0(0)		
Others	6(16.2%)	2(11.8%)		
Term of steroid treatment, M (mean $\pm$ SD) Range	18.8 $\pm$ 9.8 (6–40)	21.4 $\pm$ 5.2 (18–30)	-	-
Steroid-induced ocular hypertension, n	22(59.5%)	12(70.6%)	-	-
Steroid-induced glaucoma	2(5.4%)	0		
Steroid-induced cataract	12(32.4%)	7(41.2%)	-	-

HCs: Healthy controls; SLE: Systemic lupus erythematosus; RA: heumatoid Arthritis.

Table 2
The intro-ocular hypertension, anti-glaucoma eyedrops counts and cataract occurrence timetable for patients with systemic corticosteroid treatment during 18m follow-up.

Patient No.	1 m		3m		6 m		9 m		12 m		15 m		18m	
	drugs	cataract	drugs	cataract	drugs	cataract	drugs	cataract	drugs	cataract	drugs	cataract	drugs	cataract
1	0	-	0	-	1	-	1	-	0	-	0	-	0	-
2	2	-	2	-	3	-	2	-	2	+	2	+	0	+
3	0	-	0	-	0	-	0	-	0	-	0	-	0	-
4	2	-	2	-	3	-	3		4	-	4	-	4	+
5	2	-	3	-	1	-	1	-	0	+	0	+	0	+
6	1	-	1	-	0	-	0	-	0	-	0	-	0	-
7	4	-	2	-	1	+	0	+	0	+	0	+	0	+
8	0	-	3	-	3	-	2	-	2	-	2	-	2	-
9	0	-	0	-	2	-	2	-	2	+	2	+	2	+
10	1	-	1	-	2	+	2	+	2	+	2	+	2	+
11	0	-	0	-	0	-	0	-	0	-	0	-	0	-
12	0	-	0	-	0	-	0	-	0	-	0	-	0	-
13	0	-	0	-	0	-	0	-	0	-	0	-	0	-
14	3	-	3	-	3	+	3	+	2	+	2	+	1	+
15	3	-	1	-	1	-	1	-	0	-	0	-	0	-
16	0	-	2	-	2	-	1	-	1	-	0	-	0	-
17	3	-	2	-	2	-	2	-	2	-	2	-	2	-
Total	21	0	22	0	24	3	20	3	17	6	16	6	13	7
Counts (n,%)	9 52.9%	-	11 64.7%	-	12 70.6%	3 17.6%	11 64.7%	3 17.6%	8 47.1%	6 35.3%	7 41.2%	6 35.3%	6 35.3%	7 41.2%

Table 3

pRNFL thicknesses in patients' eyes with intro-ocular hypertension compared with that of normal IOP eyes and HCs eyes

pRNFL thickness(μm)	All patients	Ocular hypertension eyes	Normal IOP eyes	HCs eyes	P1	P2	P3
Global	103.5 $\pm$ 12.0	104.9 $\pm$ 9.4	101.6 $\pm$ 15.1	100.9 $\pm$ 8.9	0.07	0.01	0.73
Temporal	87.0 $\pm$ 15.0	85.3 $\pm$ 12.6	89.5 $\pm$ 18.0	89.1 $\pm$ 14.7	0.32	0.12	0.90
Supero-temporal	151.4 $\pm$ 22.2	153.1 $\pm$ 17.1	149.0 $\pm$ 28.3	146.7 $\pm$ 16.7	0.11	0.03	0.67
Infero-temporal	155.7 $\pm$ 23.1	156.2 $\pm$ 17.1	154.9 $\pm$ 30.1	153.2 $\pm$ 20.8	0.43	0.39	0.71
Nasal	60.7 $\pm$ 14.6	64.3 $\pm$ 15.3	55.5 $\pm$ 11.9	58.0 $\pm$ 14.5	0.20	0.02	0.37
Supero-nasal	116.2 $\pm$ 23.0	117.8 $\pm$ 21.7	113.8 $\pm$ 24.9	111.7 $\pm$ 22.7	0.18	0.12	0.65
Infero-nasal	109.8 $\pm$ 22.4	112.9 $\pm$ 20.1	105.2 $\pm$ 25.0	102.0 $\pm$ 19.8	0.01	0.00	0.45

P1: All patients versus HCs;P2: Ocular hypertension eyes versus HCs;P3: Normal IOP eyes versus HCs eyes.

Figures

Figure 1

Algorithm of the included children.

Figure 2

The incidence of steroid-induced IOP hypertension and cataract in enrolled all subjects.

Figure 3

The fundus of a 16-year-old girl with SLE who was diagnosed as steroid induced glaucoma of the left eye after treated with oral steroid for 3 years. The C/D of the right eye was 0.2 and the left eye was 0.9.

Figure 4

The timeline of the number of anti-glaucoma eyedrops and cataract occurrence.