Steroid-induced cataract and glaucoma in pediatric patients with nephrotic syndrome

ABSTRACT

Objective
This study investigated ocular complications, such as cataract and glaucoma, arising from prolonged corticosteroid therapy in children.

Methods
A cross-sectional study involving pediatric patients with nephrotic syndrome was conducted in a tertiary hospital. Comprehensive ophthalmic assessments including best-corrected visual acuity (BCVA), intraocular pressure (IOP), slitlamp and fundus examination were performed. Standard automated perimetry (SAP) was also performed on patients suspected of having glaucoma. Information on renal histological diagnosis and treatment regimen in each patient was noted. Data were analyzed statistically.

Results
A total of 22 patients were evaluated. The median age at the time of examination was 9.5 years (range, 2 to 17 years). The mean age of onset was 6.9 ± 4.3 years. Twelve of the 22 patients had relapses with a mean of 1.86. The mean duration of steroid use was 28 ± 28.9 months. Eleven patients (50%) were given combined therapy (prednisone with either cyclosporine or cyclophosphamide) and 11 were given oral prednisone alone. The mean dose of steroid at the time of examination was 27 ± 26.2 mg/m²/day. Among the 22 patients, 3 (13.6%) developed posterior subcapsular cataracts. One patient developed steroid-induced glaucoma with a scotoma encroaching the central 10° visual field. There was a significant association between the duration of corticosteroid treatment and cataract formation ($p = 0.04$), but no significant association between the duration of therapy and development of glaucoma ($p = 0.45$).

Conclusions
Cataract formation was a more common complication of prolonged oral corticosteroid therapy with a prevalence rate of 13.6%. Pediatric patients with a longer duration of steroid therapy are at greater risk of cataract formation. Hence, pediatricians are advised to refer these patients to ophthalmologists for proper evaluation.

Keywords: Cataract, Glaucoma, Nephrotic syndrome, Corticosteroid therapy, Intraocular pressure
NEPHROTIC syndrome is one of the most common renal diseases in children. Corticosteroids and sodium restriction form the mainstay therapy. Although most nephrotic patients recover quickly without major sequelae, the physician must remain alert for signs and symptoms of serious complications. Considering the consequences of prolonged high-dose steroid intake, patients need to be referred to an ophthalmologist.

Cataract and glaucoma are major causes of blindness worldwide. Corticosteroids given orally, intravenously, or topically have been associated with increased risks of cataract formation and glaucoma development. It has been noted that posterior subcapsular cataracts (PSC) are more frequent in people taking steroids. Steroids, especially when taken in high doses, have multiple effects on the trabecular meshwork (TM), thereby raising the risks of glaucoma.

Studies have shown that the use of systemic steroid therapy is a risk factor for developing cataracts. PSCs have been reported in 12.5 to 60% of patients receiving long-term oral corticosteroid therapy. Long-term corticosteroid treatment among children is associated with cataract formation. The development of cataract was found to be directly proportional to the dose and duration of corticosteroid treatment. Individual susceptibility also plays a role in cataract formation.

There have been many attempts to correlate prolonged corticosteroid use with ocular complications, such as development of cataracts and glaucoma. At best, the results were conflicting.

The route of administration may influence the response of aqueous dynamics. Oppelt and colleagues found that intravenous hydrocortisone produced a minimal effect on aqueous-humor formation and outflow, while topical hydrocortisone or dexamethasone produced a marked decrease in outflow. Other studies indicated that systemic administration of corticosteroids are likely to produce an increase in aqueous production. The biphasic effect of corticosteroids may explain these conflicting results. An increase in circulating corticosteroid may cause an increase in aqueous production, while topical administration of steroids may produce a decrease in aqueous outflow.

Nephrotic children undergoing corticosteroid therapy should undergo slitlamp biomicroscopy and dilated-fundus evaluation to detect any cataract formation and evidence of raised intraocular pressure (IOP). The ophthalmologist should check the contour and color of the optic disc, any asymmetry or elongation of the cupping, and thinning of the neuroretinal rim and retinal-nerve-fiber layer on serial optic-disc photos. If possible, IOP of these children should be checked periodically.

Several diagnostic instruments have been developed to determine damage to the optic nerve, such as the standard achromatic perimetry (SAP), which is most widely used to determine functional damage in glaucoma.

This study determined the prevalence of cataract and glaucoma in children with nephrotic syndrome undergoing corticosteroid therapy at a tertiary hospital and established a correlation between the duration of steroid therapy and the development of cataract and glaucoma.

**METHODOLOGY**

This is a cross-sectional study of patients with confirmed diagnosis of nephrotic syndrome from the pediatric nephrology clinic of the University of Santo Tomas Hospital. Informed consent was obtained from the parents of these patients. A detailed history of the diagnosis of nephrotic syndrome and steroid regimen (type, dose, and duration of steroid use) was obtained from the patients’ clinical records. Eyes with a history of ocular trauma or previous surgery were excluded.

A single author performed the ophthalmic examination of the included patients, consisting of best-corrected visual acuity (BCVA) using the Snellen or illiterate E chart (for children below 4 years of age). IOP measurements with an applanation tonometer (Haag-Streit, Bern, Switzerland), and assessment of the cornea and anterior chamber with a slitlamp biomicroscope (Topcon Corp., Tokyo, Japan). The crystalline lens and fundus were examined following dilation of the pupils with 2.5% phenylephrine (Alcon, Texas, USA) and 0.5% tropicamide eye drops (Alcon, Belgium). SAP was performed on patients who were able to follow the instructions.

Data collected were collated and subjected to statistical analyses using SPSS ver. 14. Tests of associations were done at significance level of 0.5%.

**RESULTS**

A total of 22 patients were included in the study, 64% of whom were males and 36% females. The median age at the time of examination was 9.5 years (range, 2 to 17 years). The mean age of onset of the nephrotic syndrome was 6.9 ± 4.3 years. Twelve patients had relapses with a mean of 1.86. The mean duration of steroid use was 28 ± 28.9 months.

Renal biopsies were performed in 5 (21.7%) patients, 3 of whom were diagnosed with membranoproliferative glomerulonephritis and 2 with focal segmental glomerulonephritis.

Eleven (50%) patients were given combined therapy (prednisone with either cyclosporine or cyclophosphamide) and 11 were given oral prednisone alone. The mean steroid dose at the time of examination was 27 ± 26.2 mg/m²/day.

Eighteen (82%) patients developed cushingoid
features, but none had hypertension. All patients denied experiencing eye pain, tearing, or glare. Three (13.6%) had posterior subcapsular cataracts, 2 of whom were bilateral and 1 uniocular.

Seven patients underwent SAP, 5 of whom had normal visual fields. One patient had an enlarged blind spot in one eye and the other developed steroid-induced glaucoma with scotomas encroaching the central 10° visual field in the left eye. He was given antiglaucoma medications. All 7 patients had 0.2 to 0.6 cup-disc ratios and IOPs ranging from 10 to 20 mm Hg. The other patients were either too young or uncooperative to complete the test. They had cup-disc ratios ranging from 0.2 to 0.4 with IOP in the normal range.

Analysis of data showed a significant association between the duration of corticosteroid treatment and cataract formation \((p = 0.036)\), but no significant association between the duration of treatment and glaucoma development \((p = 0.45)\). There was also no significant association between the age of onset and either cataract formation \((p = 0.72)\) or development of glaucoma \((p = 0.15)\). Lastly, there was no significant association between the number of relapses and either disease.

**DISCUSSION**

Studies have shown that systemic steroid therapy is a risk factor for the development of cataract in humans. The incidence varies from 14 to 51%. This wide range may be attributed to the different clinical settings wherein steroid therapy is warranted. In this study, cataracts were seen in 3 (13.6%) of the children who received oral corticosteroid therapy for nephrotic syndrome. The results were similar to those of other studies showing significant correlation between duration of steroid treatment and cataract formation. The authors, however, cannot infer if the incidence of cataract formation was greater in children who were given steroids at an earlier age, since 1 of the patient was diagnosed with cataract at 15 years old. The cumulative dose of the steroid therapy was not included in this study owing to the inability of some parents to remember the dose given to their children.

There have been many hypotheses on how steroids induce cataract formation. Cotlier proposed that steroids gain entry into the fiber cells of the crystalline lens and then react with specific amino acid groups of lens crystalline. These alterations free protein sulhydryl groups from the disulfide bonds leading to protein aggregation and lens opacification. Steroid-induced PSCs are associated with steroids possessing glucocorticoid activity, suggesting a key role for glucocorticoid receptor activation and subsequent changes to the transcription of specific genes. Glucocorticoid-receptor activation is associated in many cell types with proliferation, suppressed differentiation, a reduced susceptibility to apoptosis, altered transmembrane transport, and enhancement of reactive oxygen species activity. There is involvement of aberrant migrating lens epithelial cells in steroid-induced PSCs. Glucocorticoids may be capable of inducing changes to the transcription of genes in lens epithelial cells that are related to many of these cellular processes. Indirectly, steroids can affect the lens through the responses of other cells within the ocular compartment. This could be mediated through alterations to the intraocular levels of growth factors that normally orchestrate lens development and maintain lens homeostasis.

Steroid-induced glaucoma is an iatrogenic secondary open angle. In a study by Sihota, the raised IOP in such eyes has been shown to lower with time after stopping steroid use. The exact mechanism by which corticosteroids cause a rise in IOP is uncertain. Some authors believe there is a decrease in the facility of outflow, others an increase in aqueous production. It has been postulated that there may be abnormal functioning of cells in the area of the trabecular meshwork leading to an abnormal or excessive deposition of mucopolysaccharides. Histopathology of steroid-induced glaucoma in humans has demonstrated an excessive deposit of acid mucopolysaccharide, or glycosaminoglycan (GAG), in the trabeculum.

Eleven patients underwent combined therapy with steroid and an immunosuppressive agent. It remains unclear if this combined therapy increased the incidence of cataract formation and glaucoma development in pediatric nephrotic patients.

A study conducted by Kaye and associates found no association between steroid therapy and ocular hypertension as opposed to the study done by Grossman et al. Only one patient in this study was diagnosed to have steroid-induced glaucoma.

The authors also tried to correlate the number of relapses with a higher incidence of cataract and glaucoma development in this study. When a pediatric nephrotic patient had a relapse, the steroid therapy was increased. This fluctuation of steroid therapy could induce cataract formation and ocular hypertension. However, no increase in cataract formation and glaucoma was seen in patients with a high number of relapses.

In conclusion, cataract formation is a more common complication of prolonged oral corticosteroid therapy with a prevalence rate of 13.6%. Pediatric patients with a longer duration of steroid therapy are at greater risk of cataract formation. Hence, pediatricians are advised to refer these patients to ophthalmologists for proper evaluation.

Further studies with larger sample size are recommended to clearly establish the correlation between...
steroid treatment and cataract and glaucoma formation and look into the possible relationship between steroid dose and the risk of cataract and glaucoma development.

References

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