Steroid Dependent and Independent Ocular Findings in Iranian Children with Nephrotic Syndrome

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ABSTRACT

Objectives: The aim of this study was to determine steroid dependent and independent ocular abnormalities in children with nephrotic syndrome (NS). Due to the relapsing nature of NS prolonged usage of corticosteroid puts the patients at the risk of ocular side effects of prednisolone. Since published data evaluating both steroid dependent and independent ophthalmic findings in children with NS is scarce, we evaluated ophthalmic findings in this group of patients according to the response to steroid.

Methods: The study population consisted of 35 patients with steroid-sensitive NS (SSNS) and 40 patients with steroid-resistant NS (SRNS). The patients who aged 2-18 years underwent ophthalmologic examination for steroid dependent and independent ocular abnormalities.

Results: The median age of patients was 7.2 years (ranged 1.2-19 years). Forty-seven subjects were men and 28 were women. Patients with SRNS had significantly higher systolic and diastolic blood pressure than patients with SSNS (p < 0.05). Forty-five out of 75 patients (60%) had either steroid dependent or independent ophthalmic symptoms. Twenty percent of the patients had steroid dependent and 29% had steroid independent ocular abnormalities. Posterior subcapsular cataract and myopic astigmatism were the most common steroid dependent and independent ophthalmologic symptoms, respectively.

Conclusions: Steroid independent eye involvements are not uncommon in NS children and should be considered especially in SRNS.

Keywords: Nephrotic syndrome, Children, Steroid, Ocular problems.

INTRODUCTION

Nephrotic syndrome (NS) is a condition characterized by significant proteinuria (50 mg/kg/d), hypercholesterolemia, hypoalbuminemia (less than 2.5 gm/dl), and edema. Categorizing patients based on their response to steroid treatment may help physicians determine prognosis. The disease has a chronic and relapsing nature. During relapses, patients receive repeated and prolonged courses of steroids. Therefore, assessing the side effects of steroid, in both steroid sensitive (SSNS) and steroid resistant nephrotic syndrome (SRNS) patients, is crucial. One of the most important side effects of corticosteroids that should be considered is eye involvement. Posterior subcapsular cataract, glaucoma, increased intraocular pressure, ptosis, mydriasis, eyelid skin atrophy, keratitis, thinning of cornea and sclera, macular pigmentation changes, epiblepharon with inverted eyelashes and repeated hordeolum exacerbations of bacterial and viral infections are associated with corticosteroid usage.1-4 Furthermore, NS is reported as one of clinical syndromes with specific eye involvements, such as Pierson syndrome, Wilms tumor-
Aniridia syndrome, and congenital NS. Strabismus, nystagmus, hypertelorism, myosis, buphthalmos and congenital glaucoma are reported as steroid independent ocular findings.5,14

Ocular side effects of steroid consumption are well described. However, there are few reports comparing the steroid dependent and independent ophthalmic findings between patients with SSNS and SRNS. Therefore, we conducted a study on NS children less than 18 years of age who received steroids for a long time.

METHODS

This cross-sectional survey was carried out on 75 patients with biopsy-proven focal segmental glomerulosclerosis (FSGS) or minimal change disease (MCD) in Alzahra Hospital from June 2009 to July 2010. All eligible patients according to the inclusion criteria, who accepted to participate in the study, were recruited. A checklist, containing demographic data, clinical findings and ophthalmologic symptoms (both steroid dependent and independent), was filled in for every patient. The initial treatment protocol was the same for all patients. It was started by oral prednisolone 40-60 mg/m²/d for 4-6 weeks in divided doses. In patients who did not respond to prednisolone after 4 weeks, this was followed by 10-20 mg/kg methyl prednisolone pulses for 3 consecutive days. In all patients, prednisolone dose was reduced to 40 mg/m² every other day for an extra 4-week course. Individuals who responded partially to prednisolone or demonstrated steroid side effects received cyclophosphamide (2-3 mg/kg/day for 2-3 months). Subjects resistant to steroid underwent kidney biopsy and then received cyclosporine 3-5 mg/kg/d (adjusted by fasting blood level). Eighteen patients with SRNS out of 35 (51%), who did not respond to cyclosporine after 6 months, received mycophenolate mofetile (MMF) 500-1000 mg/m²/d. Four doses of rituximab (375 mg/m²/dose for 4 consecutive weeks) were given to only 4 patients with SRNS who did not respond to any of the previous medications.

Inclusion criteria:

- Patients between 2-18 years of age with nephrotic syndrome having proteinuria (> 2 gr/m²/d or 50 mg/kg/d), hypoalbuminemia (less than 2.5 gm/dl) or hypercholesterolemia.
- Negative serology results for ANA, ANCA, anti dsDNA, C3, C4, CH50, HBS-Ag, anti HCV and anti HIV.
- Corticosteroid consumption for more than 6 months as the main or adjunctive part of the treatment
- Histopathology of FSGS or MCD proven by nephropathologist.
- Patients who accepted to attend the survey by signing the consent.

Exclusion criteria:

- Syndromic forms of nephrotic syndrome.
- Patients being non cooperative for full ophthalmologic examination.
- Presence of any systemic disease other than NS.

The study was approved by the local Ethics Committees of Isfahan University of Medical Sciences. Informed consents of the parents and/or patients were obtained.

Ocular Examination

Ophthalmological examination was performed for all patients by a pediatric ophthalmologist. Full ophthalmologic examination included determining visual acuity (with Snellen visual acuity chart), slit lamp biomicroscopy of the anterior segment before and after using cycloplegic drop, fundus examination and measurement of refractory errors.

Statistical analysis

Chi square and Fisher’s exact tests were used to compare the results in SPSS software version (SPSS Inc., Chicago, Illinois, USA). A p-value less the 0.05 was considered significant.

RESULTS

1- Clinical characteristics

From 75 enrolled patients, 47 patients were men and 28 were women. The male/female ratio in SSNS and SRNS were 1.33 (20/15) and 2.07 (27/13), respectively. The median age of all patients was 7.2 years, (range 1.2-19 years). Mean age of patients with SRNS was significantly higher than patients with SSNS (8.21 ± 4.9 compared with 6.2 ± 3.6 years; P < 0.05). Patients with SRNS had significantly higher mean systolic blood pressure than those with SSNS (102.5 ± 13.15 vs. 94.70 ± 10.07 mmHg; P < 0.05). In addition, mean diastolic blood pressure values in SRNS and SSNS groups were sig-
nificantly different (68.75 ± 12.33 mmHg vs. 63.02 ± 7.48 mmHg, respectively; P < 0.05).

Furthermore, the 24-hour urinary protein excretion was significantly higher in SRNS group compared with SSNS group (170.42 ± 29.77 vs. 485.75 ± 73.30 mg/day; P < 0.05).

Three patients died before the study was completed. The cause of death in 2 was severe influenza infection during epidemic crisis (H1N1 virus, proven by virus culture). The third patient died due to massive brain thromboembolism.

**Ophthalmologic findings**

Forty five out of 75 patients (60%) had either steroid dependent or independent ophthalmic symptoms. Among these patients about 20% had steroid dependent and 29% had steroid independent ocular abnormalities. Posterior subcapsular cataract followed by increased intraocular pressure was the most common steroid dependent ophthalmic involvement (Table 1). Exacerbation of infection, ptosis, mydriasis, corneal-scleral melting, eyelid skin atrophy, repeated hordeolum and keratitis were not reported among all patients.

Myopic astigmatism, as the most common steroid independent ocular finding, was seen in both groups. However, Mittendorf’s dot was only reported in SRNS (Table 2). In addition, the following steroid independent ophthalmic findings were not found in our patients: anisometric-amblyopia, retinal detachment, microcornea, aniridia and coloboma of iris.

**DISCUSSION**

In this study, we evaluated 75 children with NS (biopsy proven FSGS and/or MCD) for steroid dependent and independent ophthalmologic symptoms. The ophthalmic side effects of steroid have been known since more than 50 years ago.

Ocular side effects are not uncommon in children with NS who are prescribed to take high and prolonged doses of steroids. In fact, receiving intravenous pulse methyl prednisolone in addition to repetitive high doses of prednisolone, due to recurrent relapses of the disease, encounter the patients with the risk of steroid side effects.

Cataract is one of the most important causes of visual impairment and even blindness in elderly people. However, steroid posterior subcapsular cataract with a distinctive feature affects all ages receiving oral steroid. This steroid-limited side effect centrally located in the posterior of the lens involves abnormal migration of lens epithelial cells. Activation of glucocorticoid receptors in lens epithelial cells results in cell proliferation, decreasing apoptosis and blocking cell differentiation. Nonetheless, this side effect has not been reported in children only on inhaled steroids.

Due to prolonged usage of steroids, ophthalmic abnormalities are common in patients with NS. The most common steroid dependent ocular abnormalities in our patients were posterior subcapsular cataract followed by increased intraocular pressure (IOP). The same results were obtained by Ryan NL et al. in Philippines children. The increased IOP but not its damage is reversible. This symptom was reported as the most common finding by Mohan et al.

Corticosteroid therapy has been recognized as a risk factor for glaucoma. The possible mechanism is raising intraocular pressure due to accumulation of extracellular matrix in the trabecular meshwork which in turn increases aqueous outflow resistance. Evolving glaucoma after glucocorticoid consumption is most probable in patients with type I diabetes and/or a positive family history of glaucoma in first degree relatives.

**Table 1.** Steroid dependent ocular findings according to patients’ response to prednisolone

| Steroid dependent ocular findings | SSNS Number (percentage) | SRNS Number (percentage) | Total Number (percentage) | Significance |
|----------------------------------|--------------------------|--------------------------|---------------------------|-------------|
| Increased intraocular pressure   | 2 (5.7%)                 | 2 (5%)                   | 4 (5.3%)                  | P = 0.64    |
| Open angle glaucoma              | 1 (2.9%)                 | 0 (0%)                   | 1 (1.3%)                  | P = 0.46    |
| Posterior subcapsular cataract    | 2 (5.7%)                 | 5 (12.5%)                | 7 (9.3%)                  | P = 0.27    |
| Macular pigment changes          | 0 (0%)                   | 3 (7.5%)                 | 3 (4%)                    | P = 0.49    |
Table 2. Steroid independent ocular findings according to patients’ response to prednisolone

| Steroid independent eye involvement | SSNS  | SRNS  | Total  | Significance |
|------------------------------------|-------|-------|--------|--------------|
|                                    | Number (percentage) | Number (percentage) | Number (percentage) | |
| Exotropia                          | 0 (0%) | 1 (2.5%) | 1 (1.3%) | Not determined |
| Myopic astigmatism                 | 8 (22.9%) | 10 (25%) | 18 (24%) | P = 0.83 |
| Mittendorf’s dot                   | 0 (0%) | 3 (7.5%) | 3 (4%) | Not determined |

While epiblepharon was the most prevalent steroid dependent ocular abnormality among Japanese children, it was not reported in our patients. In our study, steroid dependent ophthalmic abnormalities were shown in both patients with SRNS and SSNS. However, the steroid dependent ocular abnormalities were not found in Turkish children with SSNS.

Although macular pigment degeneration is strongly an age-dependent disease, metabolic, environmental and genetic factors have been reported to contribute in developing chronic changes of macular degeneration. Macular degenerative changes were only found in 3 out of 40 (7.5%) patients with SRNS who received prolonged doses of prednisolone in addition to pulse methyl prednisolone.

Myopic astigmatism is one of the most prevalent refractory errors in normal population and its prevalence has been reported as high as 19.8% in different studies. This abnormality, as the most common steroid independent ophthalmic symptom, was seen in 24% of our patients which was higher than normal Iranian children. Fatih et al. found a high prevalence of myopic astigmatism in their patients, as well.

Mittendorf’s dot, a non drug-induced ocular finding, was the second most prevalent symptom in our patients which was only observed in SRNS group. The same result was shown by Fatih et al.

We concluded that a significant number of patients with NS are at the risk of corticosteroid ocular involvement. However, steroid dependent eye involvement should be considered in patients with SRNS. To determine whether steroid-independent ocular findings have a higher incidence in children with SRNS, more studies are needed.

Conflict of interest statement: All authors declare that they have no conflict of interest.

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