Corticosteroid-induced cataracts in idiopathic nephrotic syndrome

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SUMMARY The incidence and severity of posterior subcapsular cataracts were studied in 58 children with steroid-sensitive nephrotic syndrome. Eight (14%) children had cataracts. Visual acuity was normal in all but one child. There was no relationship between total dose or mean daily dose of prednisolone (corrected for body surface area) and cataract formation. Alternate-day treatment with prednisolone for an average of half the total treatment time did not prevent cataracts. These studies show there is little risk of causing permanent visual handicap in children with steroid-sensitive nephrotic syndrome, provided prednisolone treatment is carefully controlled.

Posterior subcapsular cataracts are well-known complications of long-term corticosteroid treatment. They are alleged to occur in between 5 and 60% of patients treated with steroids,1-6 and the aetiology of the cataract is unknown. It has been proposed that they occur after high doses and prolonged treatment with corticosteroid drugs.1 7 Others suggest that they occur as a result of individual susceptibility.9 9 9 Interpretation of data is hampered because the children studied had a variety of different diseases. In few studies was the dose of prednisolone corrected according to differences in body size.

Children with idiopathic nephrotic syndrome generally require large amounts of corticosteroid drugs for many years. They often develop features of corticosteroid toxicity—such as obesity and growth retardation—and may be expected to develop steroid-induced cataracts.

The purpose of this study was to determine the incidence and severity of cataracts in a homogeneous population of children with steroid-responsive nephrotic syndrome and to determine the relationship of steroid dosage to the pathogenesis. Some children in the study also received cyclophosphamide treatment because of steroid toxicity, and it was also possible to examine the effect of this treatment on the eyes.

Materials and methods

The study comprised 46 boys and 12 girls for whom the dosage and duration of corticosteroid treatment were known. Each had been referred to our clinic because of steroid-responsive nephrotic syndrome which was difficult to manage. Each was known to have, or was believed to have, minimal change histology. Details of the patients and the duration of follow-up are shown in Table 1.

Treatment had been started with standard doses of prednisolone (60 mg/m² per 24 hours) until the urine had become protein free. The dose was then reduced during the next 2 months. Any child in whom relapse was frequent was maintained on the lowest dose of prednisolone that kept the urine free from protein. When unacceptably high doses of prednisolone were needed to maintain a remission, cyclophosphamide (3 mg/kg) was given for 56 days. Some children treated before the dangers of cyclophosphamide were fully appreciated had longer courses of treatment.

The total dose of each drug was calculated from the time that treatment with it began to either the time it was stopped or to the time of the eye examination. The total duration of treatment was the sum of each individual course of treatment. Two of the 58 children received other corticosteroid drugs (triamcinolone and dexamethasone) as well as prednisolone, and in them the dose of corticosteroid was expressed as prednisolone or its equivalent.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical features and treatment when examined</th>
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<tbody>
<tr>
<td>Mean age at onset (years)</td>
<td>Boys</td>
</tr>
<tr>
<td>5-5±3-21</td>
<td>46</td>
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Ophthalmic examination

Examination of the eyes of all the children was carried out by one of us (RBH), who did not then have details of the child's previous or present steroid therapy. These examinations were made about 6–7 years after the onset of the disease when most of them were no longer receiving corticosteroid treatment. The best corrected distance visual acuity of each eye was assessed using Snellen letter charts or equivalent letter matching tests (Sheridan-Gardiner STYCAR tests), any appropriate spectacles being worn. If the vision was less than 6/6 in any eye we judged if this was due to refractive error, to amblyopia from squint, or to blurring of the retinal image as the direct effect of lens opacities. The pupils were then fully dilated with cyclopentolate (Mydrilate) 1% eye drops, and the eyes were examined in detail using the slit-lamp microscope and the direct ophthalmoscope. Particular attention was paid not only to the posterior axial subcapsular region of the crystalline lens, the classical site of steroid-induced lens opacities (Fig. 1), but also to the anterior and posterior lens capsule, and to the epicylar tissues.

The degree of the lens opacities in children with changes considered to be typical of corticosteroid-induced cataracts was classified using the four grades described by Crews10 (Table 2). We found the distinction between the grades I and II too subtle, and these two grades were therefore combined.

Results

Results of the eye examination are shown in Table 3. Eight of the 59 children had changes typical of corticosteroid-induced cataracts. In 7 of them the opacities were assigned to the combined grades I and II, and there was no evidence of reduced visual acuity. In one child the visual acuity was slightly reduced to 6/9 (20/30), and the lens changes classified as grade III. In all cases the lens opacities were similar in the two eyes. No child had Crews's grade IV opacities. The remaining 51 children had normal eyes with no lens opacities that could be attributed to corticosteroid treatment.

During the examination it was noted that 14 children, while having no opacities within the posterior subcapsular lens substance, did show some opacification within, or on, the posterior surface of the posterior lens capsule in the axial and paraxial regions. These opacities were not dot-like, but took the form of lines and swirls. They were not believed to be steroid-induced, for similar opacities are quite often noted in the posterior capsules of normal patients, representing minor developmental defects associated with the normal antenatal regression of the posterior tunica vasculosa lentis and the fetal hyaloid vascular system. In all but 2 of these children both eyes were similarly affected. In none was there any reduction in best corrected visual acuity that could be attributed to these minor opacities.

The mean prednisolone dose of the group of 14 children with minor developmental defects was identical with that of the group without lens opacities. The results of both groups were therefore analysed together as the normal group.

The effects of corticosteroid treatment on the pathogenesis of posterior subcapsular cataracts were then examined. The 7 with combined grade I and II ophthalmic opacities had received on average a total prednisolone dose of 10·5 g/m² body surface

<table>
<thead>
<tr>
<th>Grade</th>
<th>Classification of corticosteroid-associated cataracts</th>
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<tbody>
<tr>
<td>I</td>
<td>Occasional subcapsular opacity or vacuoles in the central region of the lens</td>
</tr>
<tr>
<td>II</td>
<td>Small clusters of subcapsular opacities remaining discrete</td>
</tr>
<tr>
<td>III</td>
<td>Multiple clusters of subcapsular opacities which have mainly coalesced</td>
</tr>
<tr>
<td>IV</td>
<td>Extensive subcapsular opacities forming a plaque on the back of the lens and extending forward into the cortex</td>
</tr>
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Fig. 1 Typical grade IV steroid-induced posterior subcapsular lens opacities.

Table 3 Effect of alternate-day prednisolone treatment and mean daily dose (± SD) of prednisolone on the eyes of nephrotics

<table>
<thead>
<tr>
<th>Ophthalmic grade</th>
<th>Total no of patients</th>
<th>Number given alternate-day treatment</th>
<th>Alternate days % total treatment time</th>
<th>Mean daily prednisolone dose (mg/m² per day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>50</td>
<td>28</td>
<td>56·6±27·0</td>
<td>15·5±9·1</td>
</tr>
<tr>
<td>I &amp; II</td>
<td>7</td>
<td>5</td>
<td>46·6±18·4</td>
<td>10·4±7·5</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>9·4</td>
</tr>
</tbody>
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*Mean daily dose = total prednisolone dose (mg/m²)/total duration of treatment (days).
area. In contrast the child who was most severely affected had received a total prednisolone dose of only 3.56 g/m² (Fig. 2).

The mean total duration of treatment of those with normal eyes was 2-1 years (Fig. 3). Those with the combined grade I and II ophthalmic abnormalities were treated for an average of 3.8 years. In contrast the boy with grade III ophthalmic abnormalities received treatment for only 1 year.

The effects of the mean daily dose of prednisolone and alternate-day corticosteroid treatment were then examined (Table 3). The 50 children with normal eyes received on average 15.5 mg/m² per day. This was more prednisolone a day than the 7 children who had steroid cataracts, in whom the average daily dose was only 10.4 mg/m². Thirty-three children were treated on alternate days for between 16 and 83% of the total treatment time; 28 of them had healthy eyes, and had alternate-day treatment for a mean of 56% of the total treatment time. The 5 with the combined grade I and II opacities received alternate-day treatment for an average of 46.6% of the time. The only child with grade III opacities had been treated with daily prednisolone. The proportion of the total treatment time prednisolone was given on alternate days was not significantly different between those with opacities and those with healthy eyes.

Twenty-two children were treated with cyclophosphamide as well as prednisolone (Fig. 2). The main indication for cyclophosphamide treatment was severe steroid toxicity. These 22 children received more prednisolone (on average 11.56 g/m²) than the 36 treated with prednisolone alone (7.67 g/m²). Eighteen of the 22 who had cyclophosphamide had normal eyes. They were treated with an average of 7.4 g/m² cyclophosphamide and 11.9 g/m² prednisolone. The remaining 4 children treated with cyclophosphamide had the combined grade I and II opacities and yet had received less prednisolone treatment. The mean total doses were 5.3 g/m² cyclophosphamide and 10.0 g/m² prednisolone.

**Discussion**

Black was the first to report an association between posterior subcapsular cataract and steroid therapy in patients with rheumatoid arthritis. After some initial disagreement a number of confirmatory reports followed indicating that the lens opacities were the direct result of steroid toxicity, and not due to any associated inflammation, degeneration, or other process.

Special mention is made in the analysis of this series of the 14 children who, while having no opacities in the posterior subcapsular lens substance,
had some opacification within or on the posterior surface of the posterior lens capsule in the axial or paraxial region. These supplementary findings are stressed as it is possible that they may be confused with, and wrongly categorised as, true steroid-induced posterior subcapsular cataracts if great care is not taken to differentiate them by identifying their localisation entirely within or on the posterior surface of the posterior lens capsule, using high magnification slit-lamp binocular biomicroscopy.

Taking care to exclude these opacities the incidence of true steroid-induced posterior subcapsular cataracts in this study is 13.7%. Severe visual disability did not occur although one child on careful testing had slightly reduced visual acuity (6/9). This degree of visual disability is mild and would not affect a child's learning ability nor would it later put him outside the limits of vision required for driving.

The severity and incidence of cataracts in this series of children with idiopathic nephrotic syndrome contrasts with the higher incidences found in studies of children with other diseases, some of which report severe visual disability requiring cataract extraction.\(^2\)\(^4\)\(^12\) It is possible that the incidence of cataracts in this retrospective series is low because opacities which developed during prednisolone treatment may have subsequently regressed when the drug was stopped. The 8 children with lens opacities were examined on average 4-9 years, and 37 of the 50 children without lens opacities 3-4 years, after prednisolone treatment had been stopped. Although it is possible that opacities had regressed in this latter group of children we do not believe this would detract from the observation that there is little risk of inducing severe visual handicap in children treated with prednisolone because of nephrotic syndrome.

The pathogenesis of steroid-induced cataracts is unclear. Attempts to induce cataracts in experimental animals have been unsuccessful.\(^13\) The relationship to corticosteroid drug dosage is controversial. Some reports demonstrate a relationship; others fail to do so.\(^2\)\(^8\)\(^9\) The failure to make correction of the total prednisolone doses for differences in body size makes meaningful comparisons difficult. Our study does not demonstrate a relationship between total prednisolone dose and cataract formation if the dose is corrected for differences in body size. Moreover neither the mean total duration of treatment nor the mean daily dose of prednisolone was significantly greater in those with cataracts. Treatment with prednisolone on alternate days for an average of half the total duration of treatment did not prevent cataracts developing.

These studies support the suggestion that the individual susceptibility of the patient is important in the pathogenesis of posterior subcapsular cataracts.\(^14\) Wide variations in plasma prednisolone concentrations have been described in normal subjects taking the same oral dose.\(^16\) These different pharmacokinetics of prednisolone as well as variability of protein-binding of drugs in nephrotic patients may be important in the pathogenesis of posterior subcapsular cataracts.

Many of the children in this study were no longer taking prednisolone treatment at the time of the ophthalmic examination and it was not possible in this retrospective study to detect the presence of other features of steroid toxicity. However, as the main indication for cyclophosphamide treatment was severe toxicity, the children treated with this drug were analysed separately to give some indication of the association of cataracts with other steroid side effects. This assumption is probably valid because the children treated with cyclophosphamide generally had a much larger total dose of prednisolone. However, steroid toxicity requiring cyclophosphamide treatment was not associated with a greater incidence of cataracts.

In this study cataracts occurred after a wide range of steroid dosage and it was not possible to predict cases in which they were likely to develop. This was presumably because of variations in individual susceptibility. Slight lens opacities (Crews's grades I and II) cause no significant decrease in visual acuity and can only be identified using the slit-lamp microscope. Grade III opacities cause slight reduction in vision and can be detected using a normal clinical ophthalmoscope. The pupil is dilated and the lens observed holding the ophthalmoscope one foot from the eye. By the method of retroillumination opacities can be seen as grey or black against a diffuse red reflex from the retina. We suggest paediatricians supervising long-term steroid treatment should test the visual acuity of patients every 6 months, and whenever a reduction is detected the lens should be examined in this way. If prednisolone therapy is closely monitored the treatment of children with steroid-sensitive nephrotic syndrome should not be influenced by the concern of inducing permanent visual handicap.

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References


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