Reminder of important clinical lesson

Under pressure: an ocular complication of oral corticosteroid therapy

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Summary

We describe the case of a patient with steroid sensitive nephrotic syndrome who is admitted with headaches, eye pain and reduced visual acuity. Despite thorough investigation no cause for the pain is identified. On a subsequent admission for recurrence of her symptoms her intraocular pressures are measured, which are markedly raised. Immediate medical treatment, as well as prompt weaning of her steroid therapy avoided the need for trabeculectomy surgery. We review this case and the literature surrounding this condition in children.

BACKGROUND

Corticosteroids are potent inducers of ocular hypertension which is reversible if identified early. If left untreated, subsequent glaucomatous optic neuropathy (steroid induced glaucoma) is sight threatening and may result in irreversible damage. The true incidence of ocular hypertension in children on oral corticosteroids is uncertain; while children may be investigated for a variety of other steroid-induced adverse effects, the variability or lack of ophthalmic symptoms may deter clinicians from consideration of this diagnosis. This case and literature review highlights the importance of monitoring any child on a prolonged course of oral corticosteroids for signs of raised intraocular pressure so as to prevent potentially permanent sight loss.

CASE PRESENTATION

An 11-year-old Asian girl with frequently relapsing steroid sensitive nephrotic syndrome (SSNS) presented to the Emergency Department with a 2-week history of worsening headache, ophthalmalgia and blurring of vision. She reported frontal headaches which were worse in the mornings and exacerbated by standing or activity. The blurred vision she described as a 'halo' pattern affecting

her peripheral vision. It was noted that on presentation, the patient had been on high dose oral prednisolone (60 mg/m²/day) for over 4 weeks for her 10th relapse of nephrotic syndrome since diagnosis.

The patient is well known to the local paediatric nephrology service. She initially presented in 2003 and was diagnosed with minimal change nephrotic syndrome, which was steroid sensitive. After achieving remission, she began to suffer repeated relapses. Each was treated with high dose corticosteroids which were weaned once in remission. The previous year, the patient had complained of similar symptoms of headache, ophthalmalgia and reduced peripheral vision which also coincided with the use of high-dose corticosteroids for a nephrotic relapse. Neurologists and ophthalmologists at the time had been involved and suspecting idiopathic intracranial hypertension (IIH), performed a number of investigations (table 1). Results were inconclusive, and as her symptoms improved she was discharged from follow-up.

On this occasion, initial examination revealed that the patient appeared well, with a normal blood pressure. There was no oedema and remission was confirmed with a protein: creatinine ratio of 21 mg/mmol. Cardio-respiratory examination was unremarkable. Neurological

Table 1 Timeline of investigations performed by neurology and ophthalmology teams prior to current episode

Dates/clinical presentation	Investigations performed
May 2009: Patient presents with headache, ophthalmalgia and clinically reduced peripheral vision <i>Symptoms coincide with use of high dose steroids (60 mg, 60 mg/m²/day) for nephrotic relapse</i>	MRI and MR venogram: no focal mass lesion. Normal flow in venous sequences Lumbar puncture (LP): opening pressure 20 cm water, closing pressure 12 cm water
June 2009: Ophthalmology review. Headaches and ophthalmalgia are intermittent but still present <i>Patient is on prednisolone 20 mg alternate days (weaning dose)</i>	Humphrey testing of visual fields: globally reduced on right, normal vision on left Visual acuity 6/6 and 6/9 with glasses correction (right and left) Optic discs normal on fundoscopy
August 2009: Repeat ophthalmology review <i>Patient is on prednisolone 7.5 mg alternate days</i>	Humphrey testing of visual fields: both eyes demonstrate globally reduced peripheral vision
September 2009: Patient is no longer taking corticosteroid	Visual electrophysiology testing normal
February 2010: Ophthalmology review <i>Patient is no longer taking corticosteroid</i>	Headaches have now resolved. Discharged from follow-up

examination revealed a variable reduction in peripheral vision with normal appearances on fundoscopy. Blood results including renal function were normal. A repeat lumbar puncture (LP) was performed which revealed normal opening pressures. On further ophthalmology review intraocular pressures (IOP) were measured which were markedly raised at 36 and 38 mm Hg in the left and right eyes, respectively. Retinal examination was normal.

INVESTIGATIONS

Please see table 1 for a list of investigations performed prior to diagnosis.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis considered in this patient was idiopathic intracranial hypertension as a result of corticosteroid use. The patient underwent a number of LPs each time she presented with symptoms, which showed no evidence of raised intracranial pressure. Magnetic resonance venography was also performed to rule out venous sinus thrombosis (table 1) and an MRI to exclude space occupying lesion. In addition to this, the patient received formal visual electrophysiology testing which excluded a retinal disorder or abnormality of the visual pathway.

TREATMENT

To normalise IOP, a prostaglandin analogue was prescribed and the patient's corticosteroid dose was weaned. Within 10 days of commencing treatment, pressures had normalised to 10 mm Hg bilaterally and symptoms had improved.

OUTCOME AND FOLLOW-UP

At follow-up, IOP have remained low on treatment thereby avoiding the need for trabeculectomy surgery.

DISCUSSION

Corticosteroids are potent inducers of ocular hypertension, which is reversible if identified early. If left untreated, subsequent glaucomatous optic neuropathy (steroid induced glaucoma) is sight threatening and may result in irreversible damage.¹ Normal IOP in children have been reported to range from a mean of 11.5–13.4 mm Hg.² These values increase with age, although as an adult should not exceed 21 mm Hg. Increased IOP can occur as a result of topical, periocular, intravitreal, inhaled, oral or intravenous corticosteroid therapy.³ SSNS is often managed with repeated corticosteroid courses in order to induce and maintain remission, thereby predisposing the patient to the potential adverse effects of corticosteroid therapy.

In children there is limited information regarding the prevalence of steroid induced ocular hypertension and glaucoma. Early work by Armaly revealed a heterogeneous ocular hypertensive response to topical steroid therapy in normal adults (n=80). Depending on the increase in IOP, subjects were categorised as low (less than 6 mm Hg rise in IOP), intermediate (6–15 mm Hg rise) or high (greater than 15 mm Hg rise) responders, respectively.⁴ In total 5% of subjects were classified as high responders, with 35% demonstrating an intermediate response.

Reports suggest a greater ocular hypertensive response in children when compared with adults. Lee *et al*⁵ discovered that following eyelid surgery up to 8% of children using periocular dexamethasone reached pressures within the high responder range, while a further 56% were classified as intermediate responders (n=96, 3–16 years). Other studies have confirmed this finding.^{6,7} In addition to corticosteroid responsiveness, significant dose and age-dependent ocular hypertensive responses have been reported in children.⁶ Other studies have suggested that the degree of corticosteroid response is hereditary⁴ and that Asian ethnicity may predispose to a higher mean IOP.⁸ In the case of our patient, there was no family history of glaucoma or intraocular hypertension.

Although many studies focus on topical steroid use, few comment on the consequences of systemic administration. Extrapolating from adults, the incidence of intraocular hypertension is perceived to be lower when compared with patients on topical therapy.⁹ This, however, may be underestimated in paediatric patients on long-term therapy. Recently, Yamashita *et al*⁷ found all children on maintenance oral dexamethasone for acute lymphoblastic leukaemia demonstrated a symmetrical IOP rise of greater than 21 mm Hg, with a maximum recorded IOP of 47 mm Hg.

Corticosteroids are commonly used to manage nephrotic syndrome in childhood. To date, few studies have described ocular hypertension in this population. Hayasaka *et al*¹⁰ reported 9 of 45 (20%) patients with nephrotic syndrome developed IOP greater than 22 mm Hg during corticosteroid treatment. Conversely a study by Ng *et al*¹¹ found no evidence of steroid induced glaucoma in the paediatric population (n=31).

While ocular hypertension may be asymptomatic, signs and symptoms of steroid-induced glaucoma including peripheral field defects, 'haloes', reduced acuity, ophthalmalgia and headache can be insidious and may indicate irreversible disc damage. In children, symptoms are often inconsistent with IOP changes or altogether absent, highlighting the need for vigilance in high-risk patients.⁷ Headache is usually associated with very high or a sudden rise in IOP, for instance 50 mm Hg or above. Although pressures less than this were recorded, they may have risen intermittently to higher levels on other occasions sufficient to cause symptoms before recordings were taken. Field loss in glaucoma is associated with optic disc cupping which was not present in this case. While field testing using the Humphrey Field analyser in our patient yielded high false-negative rates (54% and 80% in right and left eyes, respectively) this can occur in glaucoma patients.¹² IIH is a well-documented phenomenon in children that may present with similar symptoms, although is recognised to occur upon corticosteroid withdrawal.¹³ Our patient had recently re-started high dose steroids for a relapse which, combined with a lack of papilloedema and normal pressures on LP made the diagnosis unlikely.

Initial treatment for steroid-induced ocular hypertension and glaucoma is cessation or weaning of steroid therapy. In some cases, topical medication or even surgery may be required. Topical α -2 adrennergics, β blockers, as well as prostaglandin analogues may be used effectively in children to reduce IOP.¹⁴ In cases refractory to medical management, trabeculectomy may be required. Younger

patients, as well as those with a higher peak IOP, are more likely to require surgery.¹⁵ SSNS and the potential for repeated corticosteroid courses place a patient at a greater risk of recurrence. Although there are no reported cases within the literature, use of a less potent corticosteroid, or a steroid sparing agent may be of benefit.

In conclusion, systemic corticosteroid use in paediatric patients with nephrotic syndrome can cause elevated IOP and subsequent glaucoma, the ophthalmic effects of which may not be fully reversible. The diagnosis itself is a challenging one; many children may be investigated for other corticosteroid side effects before glaucoma is considered; furthermore, the variability of children reporting visual symptoms may deter a clinician from further testing. This case highlights the need to be vigilant when any child is on corticosteroids for a prolonged period of time, especially on high doses. Urgent assessment should be requested when a child has symptoms of headache, visual field loss or reduced acuity. Regular ophthalmic examinations are necessary in symptomatic children as early identification may prevent visual loss. Although this complication appears to be rare in children with nephrotic syndrome clinicians should be aware of the warning symptoms that require assessment. Further prospective studies are required to identify the true incidence of ocular hypertension and glaucoma in this population.

Learning points

- ▶ Corticosteroids are potent inducers of ocular hypertension. If untreated this may progress to glaucomatous optic neuropathy, which is sight threatening.
- ▶ Children have been shown to demonstrate a greater ocular hypertensive response with corticosteroids when compared with adults. Younger children and those on high-dose steroids are most at risk of steroid-induced ocular hypertension.
- ▶ Signs and symptoms of raised intraocular pressure may include peripheral field defects, 'haloes', reduced acuity, ophthalmalgia and headache. In children these may be inconsistent or altogether lacking thereby requiring a high index of suspicion in any child on oral corticosteroids.

Competing interests None.

Patient consent Obtained.

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