

Inhaled corticosteroids, adrenal suppression and benign intracranial hypertension

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Clinical record

A 15-year-old boy developed recurrent, severe occipital headache, with vomiting, lethargy and blurred vision, after a minor head injury without loss of consciousness. The headache was dull and tense, exacerbated by activity and ameliorated by sleep, but unaffected by a change of posture. A week after the head injury, his general practitioner found him to be neurologically normal. The results of a non-contrast cerebral computed tomography scan were also normal.

Based on a history of reversible wheeze and cough, the patient had been diagnosed with asthma at 12 years of age. He was strictly compliant with his prescription of inhaled fluticasone propionate (1000 µg/day via accuhaler) and rinsed his mouth after use. As instructed, he doubled the dose of inhaled corticosteroids during acute attacks, which occurred twice a year. There were no interval symptoms. Nonetheless, his dose of inhaled corticosteroids was never reduced. Before being prescribed inhaled corticosteroids, he had been prescribed nasal steroids for allergic rhinitis and nasal polyps, but rarely required this after a successful surgical intervention. He was not taking any other medications or vitamins. A year before presentation, he had had an episode of witnessed collapse with spontaneous recovery. This was attributed to a vasovagal attack at the time.

Paediatric assessment 1 month after the head injury showed that he was lean and healthy. His weight (49 kg) and height (160.2 cm) were on the 25th centiles, and his body mass index (19 kg/m²) was on the 30th centile. His head circumference (56.8 cm) was on the 75th centile.

Neurological examination gave normal results. A Mini-Mental State Examination identified a short-term memory deficit (2/3 objects recalled). The results of a cardiovascular examination were normal except for hypertension (140/70 mmHg; > 97th centile). There were no renal bruits. Urinalysis gave normal results. He was clinically euthyroid, and had no cutaneous hypo- or hyperpigmentation or signs of Cushing syndrome.

He was diagnosed with postconcussion syndrome and reactive hypertension. An ophthalmological assessment identified normal visual fields and acuity and no papilloedema. The fluticasone propionate dose was reduced to 500 µg/day with a view to gradually stopping it altogether.

Over the following 2 weeks, his headache worsened in intensity and frequency. An electroencephalogram and cerebral magnetic

resonance scan were normal. Amitriptyline (25 mg/day) was prescribed for the headache, without effect. Two months after the paediatric assessment, lumbar puncture, performed under chloral hydrate sedation when relaxed with the back fully extended, showed an elevated cerebrospinal fluid (CSF) opening pressure of 24 cmH₂O (reference range, 10–20 cmH₂O).^{1,2} The procedure resulted in immediate headache relief. Examination of the CSF showed no abnormalities. Benign intracranial hypertension was diagnosed and he was prescribed oral acetazolamide (250 mg four times daily). His inhaled corticosteroid therapy was discontinued.

Persistent mild hypertension (130/70 mmHg; 97th centile) was again noted on repeated occasions. The results of investigations (including renal function, urinalysis, renal ultrasound, full blood count, inflammatory markers, complement factors, antinuclear antibody, electrocardiography, chest x-ray, thyroid function, plasma renin activity, and urinary catecholamines) were normal and did not reveal a secondary cause of the hypertension. However, the morning cortisol level was undetectable (< 6 nmol/L). A morning short Synacthen test (250 µg) confirmed adrenal suppression, with a suboptimal cortisol rise from baseline of 175 nmol/L to a 1-hour peak of 275 nmol/L (reference, > 600 nmol/L). A paired adrenocorticotrophic hormone (ACTH) level was 15 pmol/L, not consistent with primary adrenal disease. In view of the adrenal suppression, he was prescribed oral hydrocortisone (20 mg three times daily) for periods of acute physiological stress.

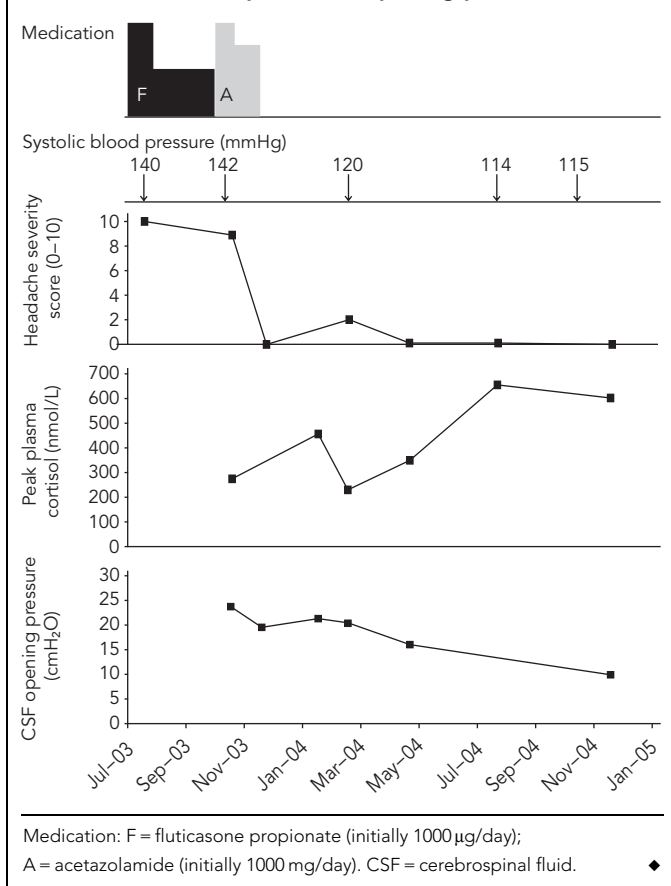
Over the ensuing months, he required multiple therapeutic lumbar punctures, with immediate headache relief on each occasion. The acetazolamide dose was ceased 2 months after initiation. His hypertension resolved 4 months after presentation and the headaches resolved after 9 months. During recovery, he used "stress" hydrocortisone for two episodes of fever and lethargy. Serial (3-monthly) morning short Synacthen tests (250 µg) were performed. By 12 months, he had a normal peak cortisol response (657 nmol/L) and a baseline ACTH level of 7.3 pmol/L. Steroid precautions were then discontinued. Ophthalmological review now identified a cotton-wool spot on the inferotemporal edge of the right optic disc, suggestive of a past axoplasmic blood flow impediment caused by raised intracranial pressure. The temporal association between his headache severity, CSF opening pressures and cortisol levels is shown in the Box. ♦

Benign intracranial hypertension has an incidence of 1 per 100 000 children.³ As "benign" belies the potentially debilitating nature of this disorder, including the risk of irreversible blindness,⁴ the synonyms "pseudotumor cerebri" and "idiopathic intracranial hypertension" are sometimes preferred. Although the pathophysiological basis has not been determined, benign intracranial hypertension has been associated with vitamin deficiencies and toxicities, obesity, head injury,⁵ adrenal insufficiency,⁶ and medications, including topical and systemic steroids.^{7–9} To the best of our knowledge, this is the first reported association between benign intracranial hypertension and inhaled corticoster-

oids (we conducted a MEDLINE search, using multiple search terms, of English language publications from 1966 to June 2005).

The diagnosis of benign intracranial hypertension in our case was based on modified Dandy's criteria, an elevated cerebrospinal fluid (CSF) opening pressure (using the paediatric reference range),^{1,2} and repeated instances of immediate headache relief with lumbar puncture. The ophthalmological findings were non-specific but supported the diagnosis. Magnetic resonance venography would have excluded venous sinus thrombosis (an important cause of benign intracranial hypertension), but there was no reason to suspect a hypercoagulable tendency.

Temporal association between headache severity, cortisol levels, and cerebrospinal fluid opening pressure



As the CSF opening pressure was first measured 2 months after the patient sustained a minor head injury, we cannot determine whether this injury was the trigger for benign intracranial hypertension or incidental to it. However, the injury alone cannot explain the benign intracranial hypertension in this patient, given its mild nature and the absence of any radiological evidence of parenchymal brain injury.

Lessons from practice

- In patients with asthma, inhaled corticosteroids should only be prescribed for those with proven frequent episodic or persistent asthma. They should be used judiciously, with a spacer, and the mouth rinsed after administration.
- The prescribed dose of inhaled corticosteroids should be the lowest that achieves symptom control. This involves regular review and "back titration" when symptoms improve.
- When discontinuing inhaled corticosteroids, especially after prolonged therapy, patients should be monitored for clinical progress and side effects, including benign intracranial hypertension.
- Benign intracranial hypertension should be included in the differential diagnosis of any patient with longstanding headache. Diagnosis of benign intracranial hypertension relies on a high index of clinical suspicion; delay in diagnosis may result in significant morbidity.

The adrenal suppression was most likely secondary to inhaled corticosteroid therapy. This is supported by the gradual adrenal recovery after withdrawal of inhaled corticosteroids. The past history of collapse suggests the onset of the adrenal suppression may have occurred 1 year before presentation.

Given the absence of papilloedema at presentation, and the fact that the headache and elevated CSF opening pressure were clearly temporally associated with the withdrawal of inhaled corticosteroids, we suggest that the benign intracranial hypertension was related to the withdrawal of the steroid dose. Benign intracranial hypertension has previously only been reported in cases of primary adrenal insufficiency (Addison disease),⁶ or in association with the use or withdrawal of topical, oral or intranasal corticosteroids.⁷⁻⁹

Clinicians should be mindful of benign intracranial hypertension as a potential side effect when prescribing inhaled corticosteroids. Our case emphasises the importance of using appropriate inhaled corticosteroid dosage and "back titration". Patients receiving inhaled corticosteroids require regular review. Dosages should be monitored to achieve the minimal dose for symptom control.¹⁰

Competing interests

None identified.

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