

CASE REPORT

Cushing's syndrome, growth impairment, and occult adrenal suppression associated with intranasal steroids

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We have previously described iatrogenic Cushing's syndrome secondary to intranasal steroids. This report further highlights the potential deleterious effects of intranasal steroids.

Nine cases (including the original two cases) are reviewed to show the varied clinical manifestations of adrenal suppression caused by intranasal steroids. Four presented with Cushing's syndrome, three with growth failure, while two asymptomatic patients were discovered in the course of pituitary function testing.

Four children had dysmorphic syndromes—Down's, Treacher–Collins, CHARGE association, and campomelic dysplasia—reflecting the vulnerability of such children to ENT problems, together with the difficulty of interpreting steroid induced growth failure in this context.

Adrenal suppression was seen not only with betamethasone but also with budesonide, beclomethasone and flunisolide nasal preparations.

A careful enquiry as to the use of intranasal steroids should be routine in children presenting with unexplained growth failure or Cushing's syndrome. Particular vigilance/awareness is required in children with dysmorphic syndromes.

We have previously described two cases of florid childhood Cushing's syndrome secondary to the prolonged use of intranasal betamethasone.¹ Since then, further cases of iatrogenic Cushing's syndrome have been reported in the literature secondary to dexamethasone² and betamethasone³ intranasal drops.

Intranasal beclomethasone dipropionate has recently been shown to adversely affect long term growth.⁴ Previous studies have documented that intranasal budesonide suppresses short term lower leg growth.⁵ Since our original report, and partly because of our increased awareness of the potential of intranasal steroids to cause problems, we have encountered a further seven patients with evidence of adrenal suppression secondary to intranasal steroids. We now present a review of these nine cases to emphasise the following: (a) the clinical manifestations of this problem include growth failure without manifest Cushing's syndrome; (b) diagnosis may be particularly difficult in children with dysmorphic syndromes, who have a higher incidence of nasal abnormalities and are thus particularly likely to receive intranasal steroids; and (c) betamethasone is only one of several intranasal preparations capable of causing adrenal suppression.

PATIENTS AND METHODS

The patients were all seen in the endocrinology clinic at the Royal Hospital for Sick Children at Yorkhill between January 1997 and 2000.

Auxology assessment included height measurement using a Holtain stadiometer, calculation of height velocity with a

preferred interval of 1.0 year, and pubertal staging according to the method of Tanner.⁶ Body mass index before and after cessation of intranasal steroids was calculated using the formula weight (kg)/height (m)². Adrenal investigation was performed using either the low dose synthetic ACTH test, as described by Crowley and colleagues,⁷ or by salivary cortisol profiles measuring two morning peaks. This technique utilises an in-house radioimmunoassay using microencapsulated antibody and ¹²⁵I-cortisol tracer,⁹ with a normal peak morning range of 5–25 nmol/l (J Schulga and A M Wallace, personal communication). Anterior pituitary function testing included growth hormone stimulation, either with arginine (0.5 g/kg intravenous infusion over 30 minutes) or insulin (0.15 units/kg intravenous bolus). Appropriate clinical photographs were obtained and are reproduced in this paper following specific parental consent.

Patients

The nine patients (six boys; three girls) were aged 1 to 16 years; table 1 shows clinical and biochemical details. Four patients had dysmorphic syndromes—Down's, Treacher–Collins, campomelic dysplasia, and CHARGE association—of whom two were receiving intranasal steroids for narrow airways and two for allergic rhinitis. The other five patients, of whom four also had asthma requiring inhaled steroids, suffered from allergic rhinitis.

Mode of presentation

Four children (cases 1–4) were referred with suspected Cushing's syndrome, two of whom (cases 1 and 3) had syndromes—Down's and Treacher–Collins. Two patients (cases 5 and 6) were referred from the respiratory clinic with growth failure. Three patients (cases 7, 8, and 9) were already attending the endocrine clinic with growth problems—short stature secondary to campomelic dysplasia, complete isolated growth hormone deficiency, and CHARGE association with choanal atresia.

Diagnosis of iatrogenic adrenal suppression

Biochemical confirmation of iatrogenic Cushing's syndrome or growth failure

Case 1 was grossly cushingoid (fig 1) and an adrenal tumour was suspected. However, plasma cortisol concentrations were unrecordable with an impaired response to the low dose synthetic ACTH test. Case 2 was being investigated for growth failure with suspected Cushing's syndrome, and showed undetectable serum cortisol concentrations, with no response to insulin induced hypoglycaemia.

Cases 4, 5, and 6 were all suspected of having iatrogenic adrenal suppression. All showed impaired cortisol responses to low dose synthetic ACTH with low peak salivary cortisol

Abbreviations: ENT, ear, nose, and throat; HPA, hypothalamopituitary axis

Table 1 Clinical and biochemical details of nine children with adrenal suppression secondary to intranasal steroid use

Case	Age (y)	Sex	Past medical history	Steroid therapy			Clinical features	Cortisol (nmol/l)		Height velocity before/after diagnosis (cm/y)	BMI before/after diagnosis
				a. Nasal b. Inhaled	Dose ($\mu\text{g}/\text{day}$)	Duration (y)		a. Basal b. Peak (n>500)			
1	3.5	M	Down's syndrome Allergic rhinitis	a. Betamethasone	133	2.2	Cushingoid	a. <24 b. 144	3 / 12.1	23.9 / 16	
2	7.0	M	Allergic rhinitis	a. Betamethasone	267	1.6	Cushingoid Hypertension	a. <24 b. <24	2.5 / 9.1	23.8 / 17.4	
3	0.8	F	Teacher–Collins Bilateral choanal atresia	a. Betamethasone	66–199	1.0	Cushingoid Hypertrichosis	a. 130 b. NA	3.2 / 14.4	17.5 / 15.5	
4	4.0	M	Allergic rhinitis Asthma	a. Betamethasone b. Budesonide	133 200	0.7 NA	Cushingoid Hypertrichosis	a. <24 b. 50	NA / 10.8	23.8 / 19.6	
5	9.0	F	Allergic rhinitis Asthma	a. Budesonide b. Budesonide	800 400	4.2 6.3	Growth failure Hypertrichosis	a. 82 b. 125	2.5 / 9.5	20 / 21.8	
6	8.0	F	Allergic rhinitis Asthma	a. Flunisolide b. Budesonide	50 800–1600	3.2 5.7	Growth failure Hypertrichosis	a. 117 b. 416	3.6 / 9.0	14.7 / 15	
7	8.0	M	Campomelic dysplasia Allergic rhinitis	a. Betamethasone	267	1.4	Short stature Asymptomatic; adrenal suppression on pituitary testing Hypertrichosis	a. <24 b. <24	0.5 / 8.6	19.2 / 16.1	
8	16	M	Isolated growth hormone deficiency Allergic rhinitis Asthma	a. Beclomethasone b. Beclomethasone	500 800	NA NA	Asymptomatic; adrenal suppression on pituitary testing	a. <24 b. <24	Final height already attained	21.5 / 19.5	
9	2.0	F	CHARGE association Bilateral choanal atresia	a. Betamethasone	133	2.2	Catch up growth post-steroid therapy; retrospective diagnosis	a. NA b. NA	7.9 / 10.8	15.4 / 15.3	

concentrations in cases 5 and 6. All three children showed hypertrichosis with increased hair, particularly over the back, but only case 4 was frankly cushingoid.

Clinical diagnosis of Cushing's syndrome

Case 3 was diagnosed clinically because of a grossly cushingoid appearance with hypertrichosis (fig 2) and a clear history of prolonged intranasal betamethasone treatment for narrow nasal airways. Venous access was extremely difficult in this child and dynamic studies of cortisol secretion were waived. However, she had a borderline low basal cortisol concentration (130 nmol/l).

Chance finding during biochemical evaluation of pituitary function

In cases 7 and 8 adrenal suppression was an unexpected finding during the course of anterior pituitary function testing. Case 7 underwent arginine, standard synthetic ACTH, LHRH, and TRH tests as part of anterior pituitary assessment prior to a trial of growth hormone therapy for extreme short stature associated with campomelic dysplasia. Case 8, who had achieved final height and full secondary sexual development, was undergoing repeat testing of the hypothalampituitary axis (HPA) to assess the severity of his growth hormone deficiency and to confirm that this was indeed isolated. In both cases plasma cortisol values were less than 24 nmol/l throughout testing. On re-examination neither had features of Cushing's syndrome, although case 7 was noted to have hypertrichosis.

Auxological diagnosis

Case 9 was diagnosed on purely auxological grounds, and then only in retrospect. Aged 2.3 years the height velocity, which



Figure 1 Case 1: child with Down's syndrome showing cushingoid features secondary to intranasal steroid use.



Figure 2 Hypertrichosis of the back caused by excessive intranasal steroid use in case 3.



Figure 4 Regression of cushingoid features in case 1 after intranasal steroid therapy discontinued.

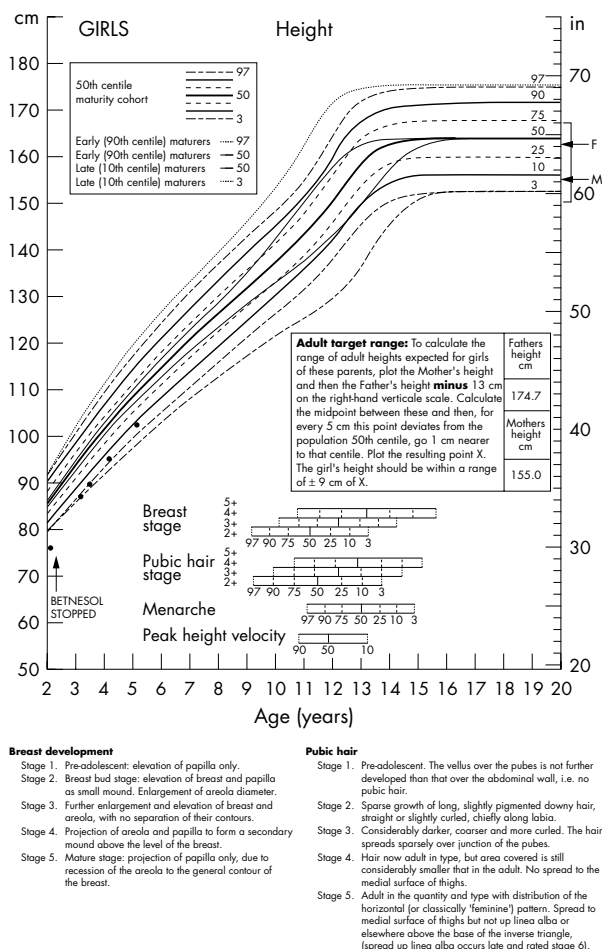


Figure 3 Buckler-Tanner growth chart showing improvement in height centile after cessation of intranasal steroid therapy in case 9.

had been carefully monitored in view of the diagnosis of CHARGE association, underwent a sudden and unexpected improvement (fig 3). On further questioning this coincided with discontinuation of betamethasone nose drops, which had been administered over a two year period.

Mode and preparation of steroid treatment

All patients were receiving intranasal steroids. Seven of these were receiving intranasal steroids for allergic rhinitis, the other two children, with Treacher-Collins syndrome and CHARGE association respectively, because of narrowed airways. Four of the nine children had a co-diagnosis of asthma and were also receiving inhaled steroids when adrenal suppression was diagnosed.

Seven of the patients had received intranasal betamethasone, which was replaced by flunisolide in one. The other two patients received budesonide and beclomethasone. Table 1 shows the duration of therapy and the daily dose (estimated by parents).

Outcome after cessation of nasal steroids

Following discontinuation of nose drops, all cases except case 8 (who had achieved final height) showed an increase in height velocity. The cushingoid features in cases 1, 2, 3, and 4 regressed (see case 1, fig 4). The index (first two) cases of iatrogenic Cushing's syndrome had normal adrenal function on dynamic testing after withdrawal of intranasal steroids. Clinical parameters (catch up growth, resolution of cushingoid features) were utilised to assess recovery of the HPA axis for patients 3-6. After withdrawal of intranasal steroids, patient 7 had a normal peak cortisol with the low dose synthetic ACTH test, and patient 8 had repeat anterior pituitary function testing which confirmed resolution of his adrenal failure, with a peak cortisol of 682 nmol/l, and isolated growth hormone deficiency, believed to be familial since a younger sibling is also affected.

DISCUSSION

This series of nine patients confirms our previous observation¹ and that of others,^{2,3} that intranasal steroids can cause adrenal suppression. In our series, however, not only is betamethasone implicated, but also beclomethasone, budesonide, and flunisolide.

While adrenal suppression was suspected in six cases, four with cushingoid features and two with growth failure, the diagnosis was discovered accidentally in two patients during anterior pituitary function testing, and recognised retrospectively in one child following unexpected catch up growth on cessation of a two year course of intranasal steroids. The diagnosis of adrenal suppression was of particular relevance to the boy with campomelic dysplasia and extreme short stature (case 7) whose mild hypertrichosis and poor linear growth had been attributed to his underlying dysmorphic syndrome and who was about to embark on a trial course of growth hormone treatment. On discontinuation of betamethasone nose drops he showed good catch up growth (height velocity increasing from 0.5 to 8.6 cm/y) making growth hormone therapy unnecessary. Case 8, who had already attained final height, exhibited no symptoms of adrenal suppression other than fatigue. While the diagnosis was fortuitous in cases 7 and 8, we speculate that they would have presented in due course with unexpected hypoglycaemia or with weight loss as described by Patel and colleagues.¹⁰ Clearly, affected children may have few or no symptoms, therefore heightened physician awareness is necessary in order to detect the early, subtle clues of adrenal insufficiency.

Given recent data that even "conventional" doses of inhaled corticosteroids used for the treatment of asthma can cause symptomatic adrenal suppression in certain children, reflecting individual variation in sensitivity to glucocorticoids,¹⁰ it is of interest that four children in this series also received inhaled corticosteroid therapy. Three of these received daily doses within the range generally regarded as unlikely to cause adrenal suppression or other significant side effects.¹¹ The maximum "safe" daily dose of budesonide is reported to be 400 µg for children and 1600 µg for adults, equivalent to 400 µg beclomethasone for children and 1500 µg for adults. Cases 4 and 5 received 200 µg and 400 µg of budesonide per day, respectively, while case 8 received 800 µg beclomethasone per day, which is still within the recommended range as he was 16 years of age. The fourth child, case 6, treated with inhaled corticosteroids received a more generous dose, ranging from 800 µg to 1600 µg budesonide per day. It is therefore likely that there was a cumulative effect of inhaled and intranasal steroids in this patient. Given that height velocity increased to within the normal range after discontinuation of intranasal steroids (except case 8 who had achieved final height) and that adrenal function normalised, it is likely that the intranasal rather than inhaled steroids were responsible for the adrenal suppression in these four cases.

When assessing children with short stature and/or growth failure it is important to take a detailed history of medications and ask specifically about the use of any steroids, whether topical, inhaled, intranasal, or oral. We would also advocate awareness of early clinical manifestations of steroid excess, such as hypertrichosis, which appears to have a predilection for the lower back.

It is particularly important to be vigilant when the child has a dysmorphic syndrome. This is partly a result of the fact that children with some dysmorphic syndromes are particularly

likely to have ear, nose, and throat (ENT) problems necessitating steroid treatment. Furthermore, it is easy to attribute poor linear growth to the underlying condition, as many syndromes are associated with an inherent tendency towards short stature and exogenous obesity, which renders it more difficult to detect the early and subtler signs of corticosteroid excess.

When adrenal suppression from intranasal steroids is suspected, the most appropriate and widely available test is the low dose synthetic ACTH test. A non-invasive alternative is the measurement of cortisol in salivary profiles, but currently this assay is not routinely available.

We acknowledge that intranasal steroid treatment has an important place in the management of selected children, particularly those with abnormal airways (for example, because of choanal atresia). However, if treatment is contemplated for longer than six weeks we recommend the following: specialist ENT review; careful monitoring of linear growth; and serial physical examination to detect the clinical features of steroid excess.

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