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Growth Failure Due to Inhaled Corticosteroid Therapy

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Case Report

A 10-year 10-month-old male was referred for evaluation of short stature. He had grown at approximately 50th percentile for height until 3 years before the visit. His parents then noted decreased growth rate on home measurements compared with his younger brother with essentially no change over the past 18 months. There were no other symptoms. Past medical history was notable for allergies and mild asthma for which he took loratidine, montelukast, and fluticasone. He had taken fluticasone for 3 years, initially 88 µg twice a day for 1 year, and 220 µg twice a day subsequently. His mother was 60 inches (152.4 cm) and dad was 70 inches (177.8 cm) tall, giving mid-parental height 67.5 inches (171.5 cm). Prior growth records at 9 years of age showed height 127 cm (14th percentile, Figure 1).

Initial height at our office was 128.1 cm (1.6 percentile), and weight was 24.8 kg. Physical exam was entirely normal with no Cushingoid features. Laboratory tests including electrolytes, sedimentation rate, thyroid function, insulin-like growth factor 1, and celiac screen were normal. Bone age was delayed at 8 years 6 months. Four months later, the height was unchanged at 128.0 cm (0.7 percentile). One microgram adrenocorticotrophic hormone (ACTH) stimulation test showed baseline and 20-minute cortisol concentrations <1 µg/dL (normal peak response >20 µg/dL¹), indicating florid adrenal insufficiency (AI). He was weaned off fluticasone over 3 months and prescribed “stress dose” hydrocortisone as needed for illness/fever.

At follow-up 6 months later, he felt well with no symptoms of AI. His asthma was controlled with just montelukast and loratidine with only one flare up that did not require prednisone treatment. Physical exam remained normal. His height was 131.9 cm (1.4 percentile, interval height velocity 7.8 cm/year). One microgram ACTH stimulation test showed baseline cortisol 4.3 µg/dL and 20 minute peak 12.9 µg/dL. Given that the patient experienced growth failure on fluticasone therapy with complete suppression of the adrenal axis and otherwise normal screening labs, then supranormal growth after

the fluticasone was weaned with an improved, though still subnormal, response to ACTH testing, it was felt that he had iatrogenic Cushing’s syndrome from systemic absorption of inhaled corticosteroid (IC). He was kept on hydrocortisone as needed.

At follow-up another 8 months later, the height was 136.5 cm (2.7 percentile, height velocity 9.2 cm/year). One microgram ACTH test showed baseline cortisol 6.2 µg/dL and 20-minute peak 13.5 µg/dL. Finally, follow-up at 12 years 8 months of age (19 months after stopping fluticasone) showed height 142.6 cm (7th percentile, height velocity 13.3 cm/year). One microgram ACTH test showed baseline cortisol 4.8 µg/dL and 20-minute peak 21.5 µg/dL. “Stress dose” hydrocortisone was discontinued, and the patient was discharged from clinic.

Discussion

Several factors influence the degree of systemic effect of IC, including potency of binding to the glucocorticoid receptor, mode of delivery, differences in pharmacokinetics, and particle size.² It is generally agreed that doses of any IC <200 µg/day are safe and cause no adrenal suppression or growth delay. In doses of 200 to 400 µg/day, most short-term and long-term studies have also shown no systemic endocrine effects,² though one study reported slight adrenal suppression in a child taking beclomethasone in this dose range.³

However, several prospective studies have shown a high risk of AI in children taking >400 µg/day of IC. The largest report⁴ evaluated 192 children taking >500 µg/day of fluticasone. They found 104 (54%) to have a normal adrenal response, 82 (43%) an impaired response, and 6 (3%) a flat response to a 1-µg ACTH test. Of note, neither was a correlation found between total fluticasone dose and height Z score nor was there a significant difference

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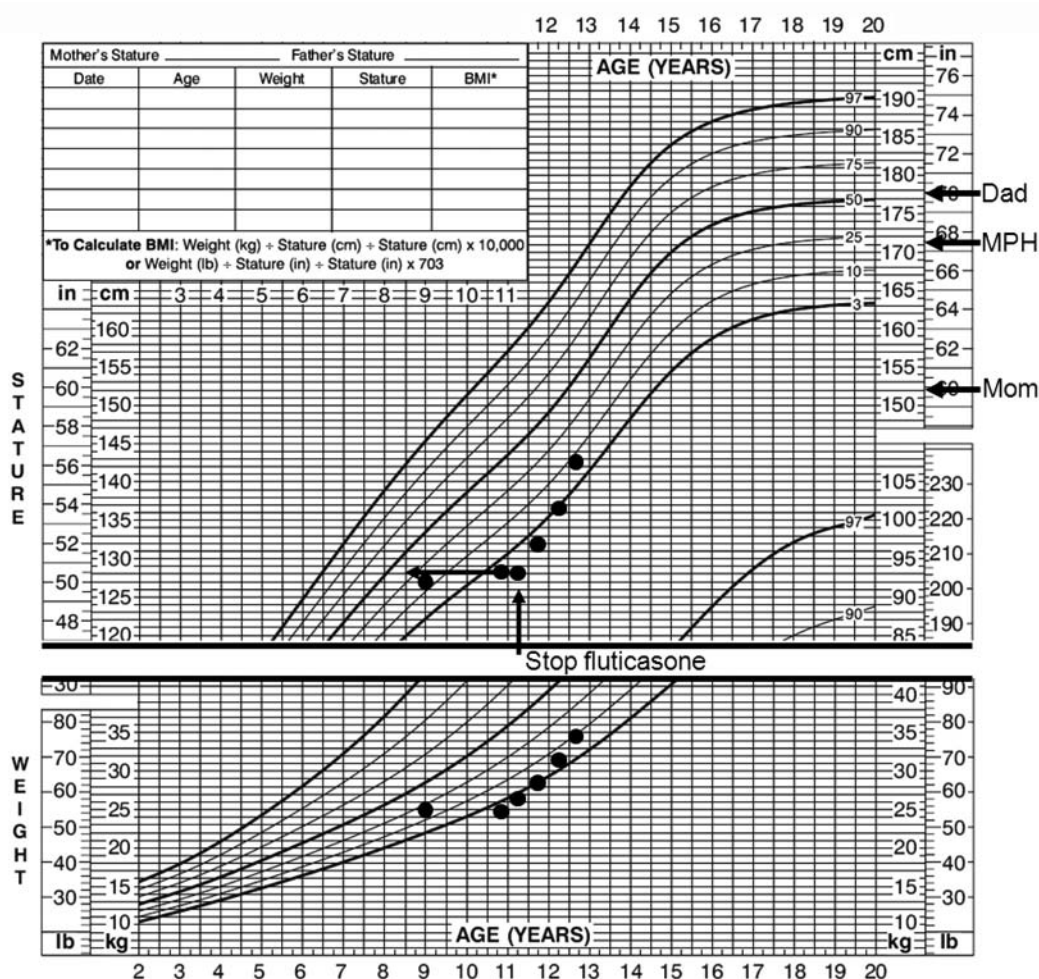


Figure 1. Growth curve for patient during and after stopping fluticasone therapy. Horizontal arrow on curve indicates bone age.

between the child's height Z score and the mid-parental height Z score. Another study followed 35 prepubertal children treated with 1000 µg/day of budesonide for 1 year.⁵ In all, 16 of the 35 children (46%) failed a 1-µg ACTH test, but there was no difference in the change in mean height Z score over the 6 months or 12 months leading up to the ACTH test between the subjects who had normal adrenal function versus those found to have AI.

Short-term and long-term effects of IC on linear growth are also fairly well described. At a daily dose of approximately 400 µg, height velocity is reduced by 0.5 to 1.5 cm/year over the first year of therapy.⁶⁻⁸ However, long-term observation after 4 to 9 years of treatment with budesonide has shown that growth rate normalizes after the first year,⁷

adult height is unaffected,⁶ and there is no relationship between dose or duration of therapy and the difference between measured and target adult height.⁶ We were only able to find one case report of a child who had decreased height velocity on IC where an ACTH test was done.⁹ This child grew at approximately 3 cm/year for 2 years while on 600 µg of fluticasone daily, and she was found to have a "flat response" to ACTH testing. After stopping fluticasone, she had "normalization" of her adrenal function and improvement in growth rate to 9 cm/year. We could only find one other report where a child on IC did not grow at all, in this case over a 3-month period.¹⁰ Similar to our patient, this child did not have any Cushingoid features. When the dose of IC was decreased, height velocity increased to ">90th percentile."

It is unclear why our patient had such pronounced AI and growth failure on a medium–high dose of IC. One possibility could be supratherapeutic serum levels of fluticasone due to inadequate clearance of the drug. Fluticasone is metabolized by the enzyme cytochrome p450 3A4¹¹ in the liver to 17- β -carboxylic acid, which has minimal affinity for the glucocorticoid receptor. It has been shown that if fluticasone is co-administered with an inhibitor of p450 3A4, such as ritonavir, serum concentrations increase by approximately 25-fold.¹² It is possible that our patient had an undiagnosed defect of this enzyme. However, we did not measure a fluticasone level, so this remains speculative. Of note, loratidine and montelukast (his other prescribed medications) are not metabolized by p450 3A4.

In conclusion, AI is common in children treated with high-dose IC. Practitioners who prescribe these medications should be aware of their effect on the adrenal axis. Whereas short-term mild growth delay is common in children taking IC, growth failure is quite rare, even in children with florid AI. Thus, monitoring of the growth rate should not be used to determine who should have screening and/or treatment for AI.

Declaration of Conflicting Interests

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