

## Iatrogenic Cushing Syndrome in a Child With Congenital Adrenal Hyperplasia: Erroneous Compounding of Hydrocortisone

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**Context:** Patients with 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) require lifelong treatment with glucocorticoids. In growing children, the drug of choice is hydrocortisone. Commercially available hydrocortisone tablets do not conform to very low doses prescribed to infants and toddlers, and compounded hydrocortisone is often dispensed to meet therapeutic needs. However, safety, efficacy, and uniformity of compounded products are not tested. We report a case of Cushing syndrome in a child with CAH who was inadvertently receiving excessive hydrocortisone in compounded form.

**Design:** A 20-month-old girl with CAH developed growth deceleration, excessive weight for length, irritability, increased facial fat, plethora, and excess body hair while receiving hydrocortisone from a local compounding pharmacy. The signs and symptoms persisted despite decreasing hydrocortisone dose. Iatrogenic Cushing syndrome was suspected. The prescribed hydrocortisone capsules were sent for analysis to the Sports Medicine Research & Testing Laboratory, where testing revealed that each 1-mg hydrocortisone capsule contained five to 10 times the dose prescribed and listed on the label.

**Conclusion:** Physicians must be aware that errors in compounded medications may lead to unanticipated adverse effects. Iatrogenic Cushing syndrome should be suspected in any child receiving compounded glucocorticoid treatment who develops growth arrest and excess weight gain. (*J Clin Endocrinol Metab* 103: 7–11, 2018)

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders characterized by impaired cortisol synthesis, and in ~75% of cases, impaired aldosterone synthesis. The treatment of CAH is challenging. The goal of therapy is to reduce excessive androgen secretion by replacing the deficient hormones. Proper treatment with glucocorticoids and mineralocorticoids prevents adrenal crisis, and allows for normal growth and development. During childhood, the preferred glucocorticoid is hydrocortisone because its short half-life minimizes the adverse side effects of more potent longer-acting glucocorticoids, especially growth suppression and excess weight gain (1).

During early infancy, reduction of markedly elevated adrenal sex hormones often requires hydrocortisone doses up to ~30 mg/m<sup>2</sup>/d, but typical childhood maintenance dosing is 10 to 15 mg/m<sup>2</sup>/d (1). The usual starting hydrocortisone dose for neonates is 2.5 mg three times daily, with adjustments made within the first few weeks of life, most often to lower doses. As commercially available tablet sizes (5 mg, 10 mg) do not conform to dosages below 2.5 mg, common practice is to provide crushed, weighed hydrocortisone tablets from a compounding pharmacy. Such products are not subject to regulatory processes. Periodic consistently timed testing of serum adrenal steroid levels, electrolytes, regular assessment of

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Abbreviations: 17-OHP, 17-hydroxyprogesterone; CAH, congenital adrenal hyperplasia; FDA, Food and Drug Administration.

patients' length/height, weight, blood pressure, and physical examination are means by which clinicians monitor for adverse effects and efficacy of treatment.

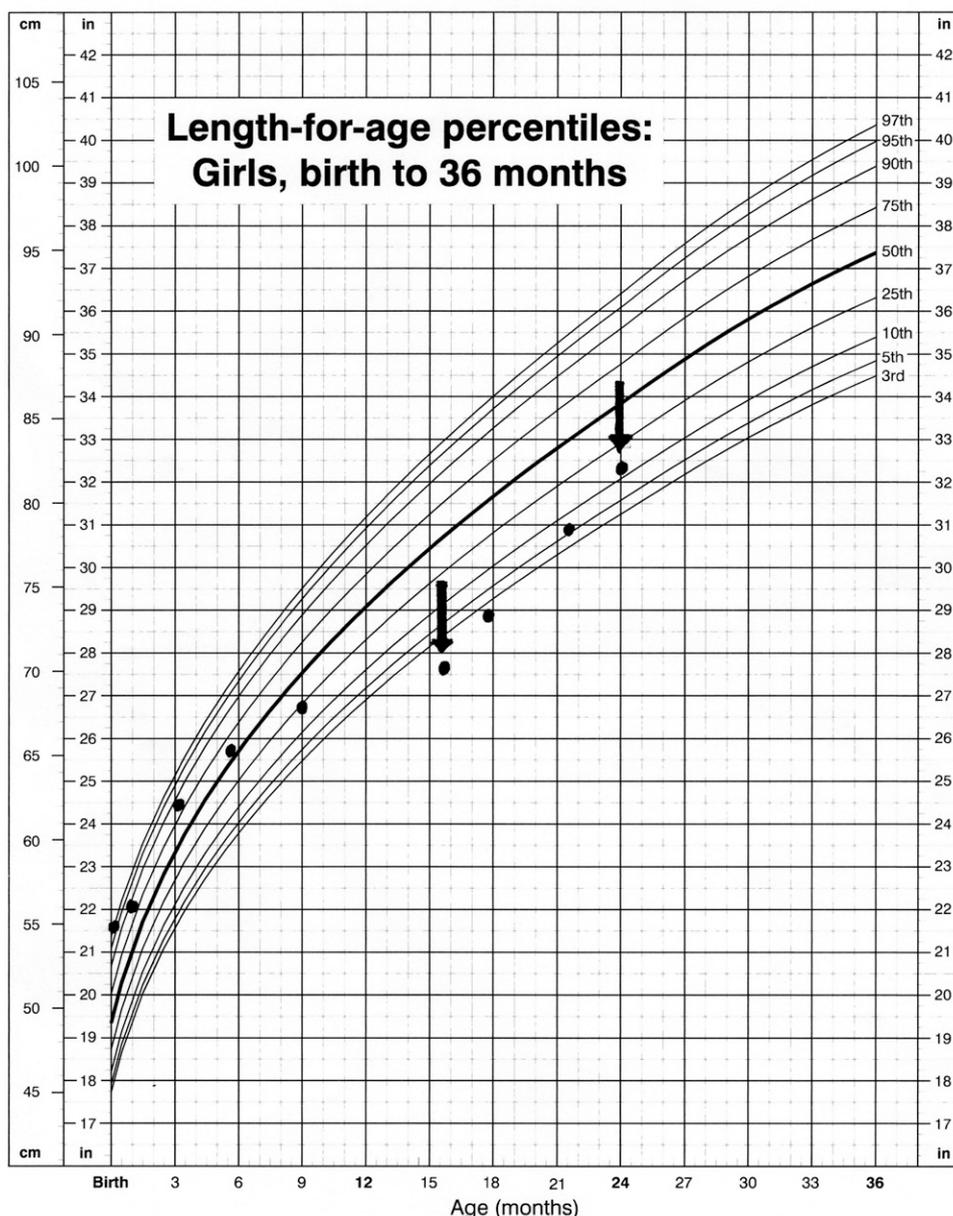
We report a case of an infant with CAH and iatrogenic Cushing syndrome resulting from inadvertent excess administration of compounded hydrocortisone.

## Case

A 2-year-old girl with classic salt wasting CAH was born at full term with atypical genitalia. The diagnosis of

21-hydroxylase deficiency was confirmed by hormonal and genetic tests. Peak serum 17-hydroxyprogesterone (17-OHP) was 402 nmol/L (13,300 ng/dL) following adrenocorticotrophic hormone stimulation. *CYP21A2* genotype showed a paternal 30 kb deletion in trans with maternal Arg357Trp. Treatment was begun on day 2 of life with hydrocortisone 2.5 mg three times daily (~31 mg/m<sup>2</sup>/d), fludrocortisone 0.1 mg twice daily, and sodium chloride 250 mg four times per day. Serum 17-OHP, testosterone, androstenedione, and renin plasma activity were measured periodically by liquid chromatography-mass spectrometry.

## CDC Growth Charts: United States

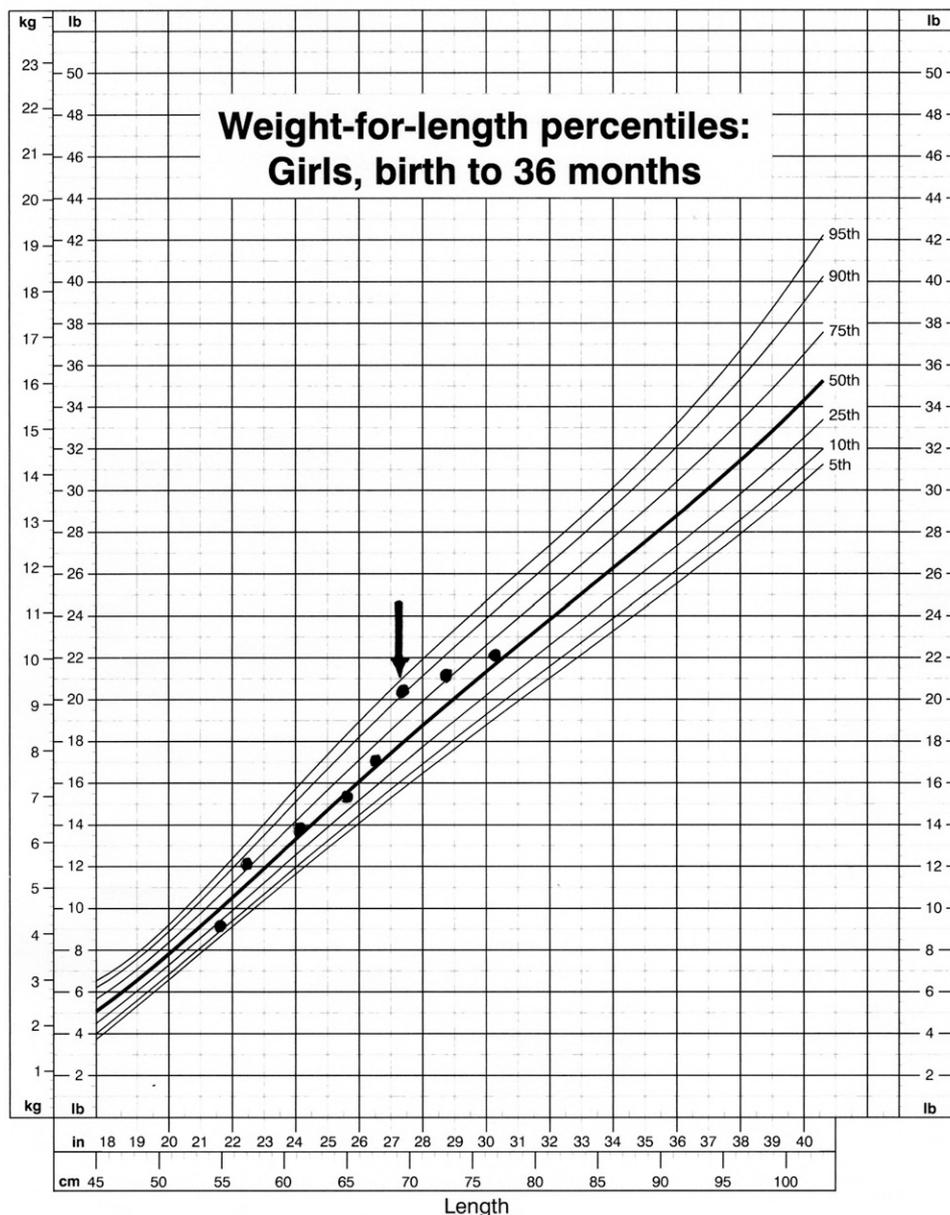


**Figure 1.** Arrows showing growth deceleration to the first percentile at age 16 months. At this point, compounded hydrocortisone was obtained from a different pharmacy. At age 24 months, the patient showed catch up growth to the 13th percentile on the new drug formulation (2). Centers for Disease Control and Prevention. Use of the World Health Organization and CDC growth charts for children aged 0-59 months in the United States. *MMWR Recomm Rep.* 2010;59(RR-9);1–15. Accessed 18 September 2017. <https://www.cdc.gov/growthcharts/data/set1/chart06.pdf>.

Hydrocortisone and fludrocortisone doses were weaned by 6 weeks of age, when her hydrocortisone was decreased to a total of 5 mg daily ( $\sim 17 \text{ mg/m}^2/\text{d}$ ) in three divided doses given as crushed and weighed hydrocortisone tablets in capsules from a local compounding pharmacy. The infant had been tracking at the 90th percentile for length for the first several months of life, but began to show growth deceleration at 6 months of age, and by 16 months of age she had fallen to the first percentile for length (Fig. 1) (2). Her weight for length was excessive at the 91st percentile (Fig. 2) and physical examination was

notable for irritability, increased facial fat, plethora, and excess body hair (2). Even with a low dose of hydrocortisone, 1 mg three times daily or  $7.5 \text{ mg/m}^2/\text{d}$ , her adrenal profile showed persistent suppression of 17-OHP and androstenedione. Imaging for an adrenal tumor proved negative. Due to strong suspicion of iatrogenic Cushing syndrome, the hydrocortisone capsules were sent for analysis at the Sports Medicine Research & Testing Laboratory in Salt Lake City, Utah. Liquid chromatography coupled with tandem mass spectrometry revealed that each hydrocortisone capsule contained as much as five

### CDC Growth Charts: United States



**Figure 2.** Arrow showing excessive weight for length at the 91st percentile at 16 months of age, with improvement after changing to a different compounding pharmacy (2). Centers for Disease Control and Prevention. Use of the World Health Organization and CDC growth charts for children aged 0-59 months in the United States. *MMWR Recomm Rep.* 2010;59(RR-9);1–15. Accessed 18 September 2017. <https://www.cdc.gov/growthcharts/data/set1/chart12.pdf>.

to 10 times the dose indicated on the label (1 mg or 2 mg prescribed), thus delivering a supraphysiologic dose of hydrocortisone. No anabolic steroids were detected. Once the medication was obtained from another pharmacy, the child's growth rate improved, and the Cushingoid features gradually resolved. This case has been reported to the Food and Drug Administration's (FDA) MedWatch (RCT-24696), and is under continuing investigation.

## Discussion

Pharmacy compounding plays a valuable role in providing access to medication for individuals with unique medical needs that cannot be met with a commercially available product (3). FDA-approved drugs are produced under Good Manufacturing Practice regulations, federal statutes that govern pharmaceuticals. Pharmacy compounding involves making a "new" drug whose safety and efficacy has not been demonstrated according to FDA standards.

In our patient's case, because the actual prescribed dose quantities were 1 mg and 2 mg, halving or quartering 5-mg tablets using a pill cutter would not have worked. In retrospect, altering the doses and using a pill cutter might have been reasonable. However, except for a very recent European report (4), errors in steroid dose compounding have not been described in the literature. This is an instance in which an infant developed Cushing syndrome attributable to iatrogenic hydrocortisone overdose. In many other countries, the lowest dose hydrocortisone tablet is 10 mg resulting in an even greater need to use compounding pharmacies than in the United States. Thus, this is a potential problem worldwide.

Because hydrocortisone suspension was withdrawn from the US market due to inconsistent concentrations (5), there have been newer suspending agents that may allow compounding of suspensions with satisfactory stability (6–9). The development of a new immediate release, multiparticulate granule formulation of hydrocortisone with taste-masking was shown to be well tolerated, easy to administer to neonates, infants, and children, with good absorption, and cortisol levels at 60 minutes similar to physiologic cortisol levels in healthy children (10). However, these preparations are as yet commercially unavailable. Another potential alternative to hydrocortisone compounding might be prednisolone syrup, which is widely available. This drug preparation is up to 15 times the potency of hydrocortisone and longer-acting. A direct comparison of prednisolone syrup with conventional hydrocortisone treatment in nine children (six with CAH) showed improved adrenal control, but growth suppression was also observed (11).

Pediatric endocrinologists must balance possible growth suppressive effects of carefully titrated prednisolone vs risks

of unreliable dosing from a compounded hydrocortisone preparation, the increased expense of compounded medication, or lack of access to a reliable compounding pharmacy.

## Conclusion

This case report should raise awareness of the possibility of iatrogenic Cushing syndrome in patients inadvertently receiving supraphysiologic doses of compounded hydrocortisone. When using individualized drug preparations to meet patients' needs, one must query the product's identity, strength, quality, and purity, particularly in the setting of side effects or inability to achieve disease control. Furthermore, this serious adverse event highlights the need for development of pediatric-specific glucocorticoid formulations, including dosing forms that would obviate frequent dose administration.

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