

Adrenal suppression: An under-recognized complication of a common therapy

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A five-year-old girl presented to the emergency department with a seizure. A bedside glucose measurement confirmed that she had hypoglycemia (blood glucose level of 1.6 mmol/L). A venous blood glucose measurement confirmed the bedside result. The seizure resolved with the administration of intravenous dextrose and phenobarbitol.

She had a three-year history of asthma for which she had been prescribed a fluticasone inhaler and instructed to take two puffs, morning and night (500 µg/day). During asthma exacerbations, her parents were administering extra doses. She had not received any oral glucocorticoids (GCs). In the months preceding presentation, she had been mildly fatigued but otherwise well. There was no identified precipitating event (eg, fever or acute illness); there were no missed doses of fluticasone.

On physical examination, the girl appeared small but well. Her weight and height had fallen from the 25th percentile to the 10th percentile over the course of one year. She was not cushingoid and her skin was not hyperpigmented. The examination was otherwise unremarkable. Following resolution of the seizure, venous blood gas and serum electrolytes were normal; however, a urine test was positive for ketones.

Based on her history of a hypoglycemic seizure in the face of inhaled corticosteroid therapy, a first morning (08:00) cortisol level was drawn. The cortisol value was 50 nmol/L (normal levels are greater than 171 nmol/L). An endocrinology consultation was requested. Daily hydrocortisone replacement was initiated at 10 mg/m²/day, given orally in the morning. Stress dosing for illness was taught to the family. Inhaled fluticasone was stopped and the girl was started on ciclesonide. Three months later, her first morning cortisol level had normalized (220 nmol/L). Daily hydrocortisone replacement was discontinued; however, the family was advised to give stress dosing (addendum 1) of hydrocortisone for illness while awaiting a low-dose adrenocorticotropic hormone (ACTH) stimulation test (addendum 2), which would be conducted a few weeks later. Her cortisol level peaked at 550 nmol/L. Stress dosing was discontinued. One year later, her asthma was well controlled and her height had returned to the 25th percentile.

LEARNING POINTS

- Adrenal suppression (AS) is a cortisol deficiency due to exposure of the hypothalamic-pituitary-adrenal axis to exogenous GCs, which can persist for up to one year after cessation of GC therapy.
- AS is a clearly proven, yet under-recognized, complication of most forms of GC therapy, including but not exclusive to oral, intravenous, inhaled, topical, intralesional, intra-articular and intramuscular therapies.
- This condition may go undetected until an illness or other stress precipitates an adrenal crisis. Many children with AS have nonspecific symptoms, such as anorexia, weakness, fatigue and lethargy.
- AS can be associated with significant morbidity, including poor response to illness, hypoglycemic seizure, coma and even death (adrenal crisis). More than 60 recent cases of AS have been described in the literature.
- Risk factors for the development of AS have not been clearly established; however, timing, higher doses and longer duration of GC therapy are associated with increased risk. Examples include the following:
 - GCs given in the evening rather than morning;
 - multiple daily dosing;
 - two or more weeks of supraphysiological (greater than 10 mg/m²/day) doses of oral/intravenous GC; and
 - greater than 500 µg of inhaled fluticasone (or equivalent) per day.
- Prevention: Morbidity of AS may be reduced by the following:
 - recognizing children at risk;
 - gradually tapering the GC dosage to facilitate recovery of the hypothalamic-pituitary-adrenal axis;
 - administering an inhaled corticosteroid with minimal systemic side effects (eg, ciclesonide [addendum 3]); and
 - administering higher doses of GCs during times of stress in children with identified AS.

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- Diagnosis
 - The low-dose ACTH stimulation test (addendum 2) is now considered to be the best test for diagnosing AS in children.
 - A first morning (08:00) measurement of cortisol level is a more practical and reasonable first step in the identification of cases of suspected AS.
 - The cortisol level should be determined at the time of hypoglycemia, especially in patients with a history of GC use.
- Management
 - When higher GC doses are no longer needed for their underlying condition, patients with AS should be treated with a physiological dose of hydrocortisone (8 mg/m²/day to 10 mg/m²/day) given in the morning. This will allow for recovery of the hypothalamic-pituitary-adrenal axis.
 - Patients with AS, and their families, should be taught 'stress dosing' (addendum 1) to simulate the protective endogenous elevations in cortisol levels that occur with physiological stress (eg, illness or surgery).
 - If possible, cases of AS should be managed in consultation with a paediatric endocrinologist.

RECOMMENDED READINGS

- Barnes NC. The properties of inhaled corticosteroids: Similarities and differences. *Prim Care Respir J* 2007;16:149-54.
- Einaudi S, Bertorello N, Masera N, et al. Adrenal axis function after high-dose steroid therapy for childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2008;50:537-41.
- Paton J, Jardine E, McNeill E, et al. Adrenal responses to low dose synthetic ACTH (Synacthen) in children receiving high dose inhaled fluticasone. *Arch Dis Child* 2006;91:808-13.

- To determine the national incidence of AS, a Canadian Paediatric Surveillance Program study was initiated in April 2010. The study is also designed to increase awareness, document the burden of illness and describe the clinical features of symptomatic AS.

APPENDIX 1: Stress dosing of hydrocortisone is used to simulate the body's response to stress or illness. For mild to moderate illness, 20 mg/m²/day to 30 mg/m²/day of hydrocortisone is given in three divided doses. For severe illness with hemodynamic instability, 50 mg/m²/day to 100 mg/m²/day of hydrocortisone is given immediately as one dose, then divided into three to four doses over 24 h. Hydrocortisone can be given orally, intravenously or intramuscularly (in emergency situations).

APPENDIX 2: The low-dose ACTH stimulation test involves the following: administration of 1 µg cosyntropin (synthetic ACTH) intravenously; blood specimens for cortisol levels are drawn at baseline, 15 min, 30 min and 60 min to assess the function of the hypothalamic-pituitary-adrenal axis; and a peak cortisol level of less than 500 nmol/L is diagnostic of adrenal insufficiency.

APPENDIX 3: Ciclesonide is a newer inhaled corticosteroid that has little to no adrenal suppressive effects. It is currently approved in Canada for children six years of age and older.

- Shulman DI, Palmert MR, Kemp SE. Adrenal insufficiency: Still a cause of morbidity and death in childhood. *Pediatrics* 2007;119:e484-94.
- Todd GR, Acerini CL, Ross-Russell R, et al. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002;87:457-61.
- Tordjman K, Jaffe A, Trostanetsky Y, et al. Low-dose (1 microgram) adrenocorticotrophin (ACTH) stimulation as a screening test for impaired hypothalamo-pituitary-adrenal axis function: Sensitivity, specificity and accuracy in comparison with the high-dose (250 microgram) test. *Clin Endocrinol (Oxf)* 2000;52:633-40.

The Canadian Paediatric Surveillance Program (CPSP) is a joint project of the Canadian Paediatric Society and the Public Health Agency of Canada, which undertakes the surveillance of rare diseases and conditions in children and youth. For more information, visit our website at <www.cps.ca/cpsp>.