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CASE REPORT

Moderate Dose Inhaled Budesonide Disguising Symptoms of Addison's Disease in An Asthmatic Boy with Silent Celiac Disease

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Inhaled corticosteroids are first-line treatment for asthma. Moderate doses of budesonide have been supposed not to affect hypothalamic-pituitary-adrenal axis function. We report the case of a boy with asthmatic symptoms and a late diagnosis of celiac disease, in whom inhaled budesonide in a dose used in conventional asthma therapy seems to have been systemically absorbed in amounts large enough to temporarily disguise the symptoms of a developing adrenal insufficiency. Inhaled corticosteroids in a dose used in standard asthma therapy seem to have the potential of disguising a developing Addison's disease. Furthermore, celiac disease, especially if diagnosed in late childhood, may be associated with Addison's disease causing a complex symptom pattern.

KEYWORDS: Addison's disease, celiac disease, inhaled corticosteroids

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INTRODUCTION

Inhaled corticosteroids are first-line treatment for asthma. Suppression of adrenal activity, growth retardation and decreased bone mass are some potential risk factors of long-term steroid treatment in children. Inhaled budesonide in daily doses of 800–1,259 μg has been supposed not to affect hypothalamic-pituitary-adrenal axis function.[1,2] However, in some asthmatic children a moderate dose of inhaled beclomethasone dipropionate or fluticasone propionate as well as long-term treatment with 400 μg inhaled budesonide caused adrenal suppression.[3-5]

This report presents an asthmatic boy, who was periodically treated with inhaled budesonide at a dose of 400 μg a day and for periods of 1–2 weeks at a dose of 800 μg a day. The moderate steroid dose appears to have been absorbed in amounts large enough to cause significant systemic effects and disguise early symptoms of a developing Addison´s disease.

CASE REPORT

This 11-year-old boy was completely breast-fed until 6 months and partially until he was 2.5 years old. From 4 years of age he had asthmatic symptoms and allergic rhinoconjunctivitis. He was prescribed inhaled budesonide (Pulmicort Turbuhaler; 400 μg daily) for intermittent use during periods of airway infection. He did not receive any systemic or intranasal courses of corticosteroids nor any inhibitors of cytochrome P 450, such as itraconazole or clarithromycin.

Prior to presentation he had fever, periodical headache, abdominal pain and tiredness for 3 days. He had no appetite and could drink only small amounts of fluid. On presentation he was tired. The abdomen was slightly tender

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but otherwise the physical examination was normal. Serum sodium was 128 mEq/L, blood glucose 45 mg/dL (2.5 mmol/L) and CRP < 3 mg/L. Gastroenteritis was suspected. He was admitted to hospital and given intravenous rehydration. Within 12 hours he was free of symptoms, could eat and drink and his serum sodium was 132 mEq/L. He was discharged in a good general condition.

Nine months later he came to our out-patient clinic for investigation of persistent tiredness and dizziness. He had had dyspnea for several months. Gastrointestinal symptoms were denied. He had periodically taken budesonide 400 μg daily and experienced relief of airway symptoms. Expiratory rhonchi were noted on lung auscultation and asthma was suspected. However, inhalation of a β_2-agonist did not increase peak expiratory flow significantly. He was prescribed inhaled budesonide 800 μg daily. Within 4 days his airway symptoms and general condition improved. After a few weeks he stopped the medication on his own initiative.

He returned 4 months later because of persistent tiredness, poor appetite, constant abdominal pain and episodes of vomiting. For a short period he had inhaled budesonide 400 μg daily. His weight had decreased from 1 standard deviation above to 0.2 standard deviation below the mean for age and gender. He was pale and looked tired. Relevant laboratory results: SR 6 mm; CRP < 10 mg/L; Hb 136 g/L; WBC 6.5 $\times 10^9$/L; platelets 401 $\times 10^9$/L. Serum albumin and liver function tests, standard urine analysis, x-ray of the lungs and ECG were normal. Serum anti-gliadin and anti-endomysium antibody levels were substantially elevated. A small bowel biopsy was consistent with celiac disease. He was prescribed inhaled budesonide 800 μg daily and a gluten-free diet and rapidly improved. After 2 weeks the budesonide dose was reduced to 400 μg daily. During the following 2 weeks his general condition deteriorated. A psychosomatic reaction to the new celiac diagnosis was suspected. He was re-admitted. On examination his face looked pale but the skin of his chest and abdomen was hyperpigmented. The blood pressure was 90/60 mmHg. Serum sodium was 117 mEq/L, potassium 5.77 mEq/L and blood glucose 85 mg/dL (4.7 mmol/L). Serum calcium, glycosylated haemoglobin (HbA_{1c}) and thyroid-stimulating hormone were normal. The diagnosis of Addison's disease was verified by the failure of P-cortisol to respond to adrenocorticotrophic hormone (Synacthen test), increased S-IgG antibodies against 21-hydroxylase and subnormal S-aldosterone. Adrenoleukodystrophy was excluded by analysis of long-chain fatty acids. Following treatment with hydrocortisone and fludrocortisone his general condition rapidly improved, serum electrolytes were normalised and his weight increased. After 3 months inhaled corticosteroid treatment was discontinued. Spirometry was normal and there were no asthmatic symptoms. A re-biopsy after one year on a gluten-free diet showed a normal small bowel mucosa.

DISCUSSION

This boy with asthmatic symptoms and celiac disease proved to have Addison's disease. On retrospective examination of the case there are some early indications of Addison's disease. The episode of hyponatraemia and relative hypoglycemia at 11 years-of-age, which was diagnosed as gastroenteritis, is consistent with relative adrenal insufficiency triggered by an infection. Furthermore, the boy's sporadic fatigue and asthenia rapidly improved every time the dose of inhaled corticosteroids was increased from 400 to 800 μg daily. Presumably the inhaled corticosteroids were absorbed and systemically available in amounts high enough to temporarily compensate for a slowly progressive adrenal hypofunction. The Addison's disease would probably have been diagnosed earlier had the boy not been treated with inhaled corticosteroids. To our knowledge this side effect of inhaled corticosteroid therapy has not previously been published.

Patel et al.[4] and Todd et al.[5] reported some cases of acute adrenal crisis during inhaled corticosteroid treatment in children presenting with hypoglycemia, coma and convulsions. Most of these children were treated with high dose fluticasone propionate, only two with budesonide 400 μg a day (up to 595 μg/m^2/day) for 1–5 years. The higher frequency of adrenal insufficiency in children treated with fluticasone propionate may relate to its high lipophilicity.[6] Stopping a high dose inhaled corticosteroid, reducing the dose or changing to

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a different preparation of overall lower potency may precipitate an episode of adrenal crisis.[5] It can be speculated that the Addison diagnosis is incorrect and that our patient in fact could be suffering from budesonide-induced adrenal insufficiency. However, the diagnosis of Addison's disease in our patient is verified by current endocrinological tests of adrenal function. Moreover, our patient has one of the clinical hallmarks of Addison's disease, i.e. skin hyperpigmentation. No patient with symptomatic adrenal insufficiency described by Patel et al. had this sign.

There are some indications that the device used for delivering inhaled corticosteroids may affect the steroid absorption. Inhaled budesonide administered with a dry powder inhaler rather than a pressurized metered dose inhaler has been reported to be more effective and thus involve a higher risk of affecting the hypothalamic-pituitary-adrenal axis.[7]

It can be hypothesized that the patient's celiac disease increased the risk of drug absorption in the small bowel. However, it seems likely that the untreated celiac enteropathy, if anything, would decrease drug absorption in keeping with the malabsorption of nutrients in untreated celiac disease.

Recent studies show that celiac disease is as common in the United States as in Sweden with 1 in 100 children having the disease by 5 years of age.[8-10] The association between celiac disease and other immunological diseases is well documented. Reunala et al. reported Addison's disease in 0.5% of 383 adults with celiac disease.[11] In an Italian multicenter study the duration of exposure to gluten and a late diagnosis of celiac disease were the two most important risk factors for developing autoimmune disorders in patients with celiac disease.[12] The boy was breast-fed for 2.5 years. This probably modified the course of his enteropathy leading to the late diagnosis of celiac disease, which otherwise is nowadays being made in Swedish children at a mean age of 3.7 years.[8]

In conclusion, our case provides evidence that inhaled corticosteroids in a dose used in conventional asthma therapy may be absorbed and systemically available in amounts large enough to temporarily disguise the symptoms of a developing adrenal insufficiency. Furthermore our case illustrates the fact that celiac disease, especially if diagnosed in late childhood, may be associated with Addison's disease causing a complex symptom pattern and thereby difficulty in reaching a correct diagnosis.

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