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Case Report

Adrenal Insufficiency Secondary to Inhaled Corticosteroids in Children with Cystic Fibrosis

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Abstract

Background/Objective: The Cystic Fibrosis Foundation recommends against routine use of Inhaled Corticosteroids (ICS) to improve lung function in Cystic Fibrosis (CF) patients. However, in 2005, just in North America, 46% of CF patients received ICS. While several studies have reported Adrenal Insufficiency (AI) due to the use of ICS, none have looked at the causation in children with CF. In this study, we showed the association of AI secondary to ICS in CF and the need for further studies and clinical trials with the end goal of having screening for AI in this specific patient population.

Method: Retrospective, descriptive, observational method. Four CF patients with known diagnosis of AI who have received care at the University of Kansas Health System (UKHS) have been identified and their cases were reviewed. Data was collected from their chart review and from the cystic fibrosis database.

Conclusion: AI is an under-diagnosed pathology in CF patients, since its clinical manifestations are vague and it is most frequently seen in chronically-ill patients. The long-term use of ICS in CF patients should raise concerns for AI especially in the setting of frequent exacerbations or exacerbations that require multiple antibiotic therapies. More studies and clinical trials are needed to determine the need of stress dosing on this population and the effects on their lung function.

Keywords: Adrenal insufficiency; Cystic fibrosis; Inhaled corticosteroids

Significance/Background

Adrenal Insufficiency (AI) is the result of decreased hormonal production from the cortex of the adrenal gland. The diagnosis and treatment of AI in childhood and adolescence poses a number of challenges. Clinical features of chronic AI are vague and non-specific and mimic many other causes of chronic illnesses [1]. Several studies have reported adrenal suppression and growth decline associated with Inhaled Corticosteroids (ICS) in asthma patients [5,6]. However, none have looked at this association in cystic fibrosis pediatric patients or the outcome on their disease process. There have been case studies reporting adrenal suppression or crisis in cystic fibrosis patients. Two of the case studies report an association with inhaled fluticasone [9,10]. One of the case studies reports association with budesonide for treatment of ABPA [11]. However, there are no studies showing correlation between long-term ICS use and its likely effect on worsening the clinical picture in cystic fibrosis patients.

Methods

This is a cross-sectional retrospective and descriptive study. The records of four patients attending the Cystic Fibrosis clinic at the University of Kansas Healthy System (UKHS) were reviewed. The electronic medical records of the patient were accessed by the investigators to collect data for the study. The time frame for the study was 6 months. Demographic data (age and sex), CF disease genotype, pulmonary disease characteristics based on their Forced Expiratory Volume in the first second (FEV1), Comorbidities, Respiratory Regimen (including the use of inhaled antibiotic therapy), initiation of inhaled corticosteroid and type, use of systemic steroids, time of diagnosis, diagnostic study and valued obtained during test (Low dose vs High dose ACTH stimulation test). Data were collected from 1 year before diagnosis to 1 year after diagnosis of adrenal insufficiency was made (Table 1).

Case Summaries

Case 1

A 12-year-old male with a known diagnosis of cystic fibrosis (confirmed by positive sweat chloride of 85mmol/L and genotype F508del/1898+1G>A) and history of nasal polyposis, chronic rhinosinusitis, constipation, growth hormone deficiency, and Attention Deficit Hyperactivity Disorder (ADHD). He is colonized with Pseudomonas aeruginosa and Methicillin-Sensitive Staphylococcus Aureus (MSSA). Patient presented with 2 months history of cough, fatigue, significant thick rhinitis with reduced FEV1p to 78% from baseline of 108%. His pulmonary regimen consisted of inhaled Tobramycin rotating with inhaled colistin, albuterol with vest treatments four times daily, dornase alpha, inhaled fluticasone, and inhaled hypertonic saline twice daily, azithromycin three times weekly. During admission, decrease in linear growth was noted, and Pediatric Endocrinology was consulted. High dose Adrenocorticotropic Hormone (ACTH) stimulation test done, revealing peak cortisol level of <0.4 mcg/dL. Patient continued with intravenous antibiotic therapy and hydrocortisone stress dose of 5 mg twice daily was added to his regimen and continued for a total of 12 days. At discharge, there was an improvement in the patent's

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Table 1: Summary of information of each case presented in this paper. Information was obtained one year before and after diagnosis of Adrenal Insufficiency.

Case Number	Before Diagnosis of Adrenal Insufficiency			Use of ICS in months before diagnosis of AI	After Diagnosis of Adrenal Insufficiency			
	Best FEV1p	Worst FEV1p	Total Daily Dose of ICS		Best FEV1p	Worst FEV1p	Total Daily Dose of ICS	Maintenance Oral Steroids
1	109	72	Fluticasone 440 mcg	55 months	150	73	Beclomethasone 320 mcg	Hydrocortisone 5 mg BID
2	114	106	Fluticasone 440 mcg	Unknown	98	84	Fluticasone 880 mcg	Hydrocortisone 15 mg BID
3	110	81	Fluticasone 440 mcg	12 months	83	66	Fluticasone 440 mcg	Hydrocortisone 10 mg BID
4	102	88	Budesonide and Formoterol 320/18	53 months	97	84	Budesonide and Formoterol 320/18	None

symptoms and FEV1p of 98%.

Case 2

An 18-year-old male with cystic fibrosis, sweat chloride of 116mmol/L, and genotype homozygous delta F508, as well as, chronic sinusitis, Gastroesophageal Reflux Disease (GERD), diabetes mellitus related to cystic fibrosis, pancreatic insufficiency due to cystic fibrosis, bronchiectasis. He is colonized with Methicillin-Resistant Staphylococcus Aureus (MRSA), Achromobacter, and Pseudomonas. Patient had multiple previous admissions and 4 previous courses of oral steroid with improvement of symptoms. He reported 2-month history of fatigue, increase cough, chest pain, as well as excessive nasal drainage. His FEV1p was decreased to 88% from baseline of 97%. His pulmonary regimen consisted of inhaled gentamycin, inhaled fluticasone, albuterol, and dornase alfa twice daily, vest treatment four times daily. During admission, based on the history of multiple oral steroids courses, morning cortisol level was drawn and recorded at 0.4 mcg/dL. Pediatric Endocrinology recommended a High-dose ACTH stimulation test, revealing peak cortisol level of 14.6 mcg/dL. Stress dosing with hydrocortisone 25 mg three times daily for a total of 4 days was added to his regimen. At discharge, there was an improvement in the patent's symptoms and FEV1p of 94%

Case 3

A 16-year-old male with cystic fibrosis genotype 1585-1G>A/3528delC, unknown sweat chloride values, as well as status post left lower lobectomy, seizure, diabetes mellitus related to CF, pancreatic insufficiency, growth hormone deficiency. He is colonized with MRSA and Pseudomonas. At presentation, patient complained of fatigue, increased sleepiness, increase cough, worsening sputum production, and a reduction in FEV1p to 71% from his baseline of 91%. His pulmonary regimen included inhaled aztreonam, dornase alpha, hypertonic saline, and fluticasone twice daily, albuterol and vest treatment four times daily. During admission, a morning cortisol level was drawn with a value of <0.4 mcg/dL. A Low-dose ACTH stimulation test was done with peak cortisol level of 7.1 mcg/dL. After consulting with Pediatric Endocrinology, an oral steroid maintenance dose with hydrocortisone 10 mg twice daily was added to his regimen. At discharge, there was an improvement in the patent's symptoms and FEV1p of 98%.

Case 4

A 14-year-old female, with cystic fibrosis genotype homozygous delta F508, as well as chronic sinus infection, and GERD. She is colonized with MRSA and Pseudomonas. At presentation, patient with history of cough above her baseline, poor sleep, decrease appetite and activity level, fatigue, chest pain, decrease in FEV1p to 88% from her baseline of 90%. Symptoms improved while patient on 5-days oral steroid course as outpatient 12 days before admission. Her pulmonary regimen included albuterol, dornase alpha, hypertonic saline, and fluticasone twice daily, azithromycin three times weekly, and vest four times daily. During admission, morning cortisol level was 0.9 mcg/dL. Patient underwent a High-dose ACTH stimulation test with initial cortisol level of 0.9mcg/dL but peak level of 23.2 mcg/dL. Pediatric Endocrinology was consulted and decided to start stress dosing with Hydrocortisone 15 mg daily for 5 days, for moderate to severe illness since initial cortisol level was low. But based on the patient's overall test, she did not need steroid maintenance dose. At discharge, no pulmonary function tests were performed.

Discussion

Cystic Fibrosis (CF) is a chronic disorder of autosomal recessive inheritance which principally affects the respiratory tract, pancreas, gastro-intestinal tract and liver. In the respiratory tract, abnormalities result in mucus plugging the airways and increasing susceptibility to respiratory tract infection. This leads to neutrophil-dominated airway inflammation with a secondary lung damage (bronchiectasis) and, eventually, respiratory failure and death. Therefore, reduction of lung inflammation is one of the primary goals of cystic fibrosis therapy. Inhaled corticosteroids are often used to treat children and adults with cystic fibrosis [4]. The ability of exogenously administered corticosteroids causing adrenal atrophy has been proven in multiple reports [3,5,6,8]. Hypothalamic-Pituitary-Adrenal (HPA) axis suppression by exogenous glucocorticoid is not trivial and has been described with inhaled and systemic therapy [4]. Marked adrenal suppression occurs with high doses of inhaled corticosteroid above 1.5 mg/d (0.75 mg/d for fluticasone propionate) [8]. Meta-analysis has shown significantly greater potency for adrenal suppression with fluticasone compared with beclomethasone dipropionate, budesonide, or triamcinolone acetonide [8]. To date, the High-dose stimulation test with cosyntropin is the most commonly used and considered a first line investigation to confirm the diagnosis of adrenal insufficiency [2]. The Cystic Fibrosis Foundation recommends against routine use of Inhaled Corticosteroids (ICS) to improve lung function or prevent exacerbation in patients without asthma or Allergic Bronchopulmonary Aspergillosis (ABPA). This a Grade D recommendation which indicates that the certainty of no benefit is high. While more recent data from United Kingdom Cystic Fibrosis Registry (UK CFR) shows that in 2007, 21% children under 16 years and 23% adults were prescribed regular ICS; and North American data from the CF registry showed that in 2005, 46% patients received ICS [7]. It is clear that more and more CF patients are using ICS. Current guidelines recommend annual screening and surveillance for cystic fibrosis related diabetes, bone disease, fat soluble vitamin deficiencies, but no AI. However, based on the statistics of ICS use in

CF population and the reported side effects of ICS in asthma patients; it appears that the CF patient population maybe be under screened when it comes to concerns of adrenal suppression.

Conclusions

It has been well-described the multiple complications of inhaled corticosteroids, mostly focused on linear growth or glucose metabolism. To the best of our knowledge there are no previous reports of adrenal insufficiency in pediatric patients with cystic fibrosis. With this case series, we are trying to raise awareness of its incidence, as well as, the nature of the symptoms which are vague and common in chronically ill patients. Patients on ICS, mainly fluticasone, that present with fatigue, multiple pulmonary exacerbations that fail to improve with mainstay treatment, should raise suspicion for an underlying adrenal cause. Our main goal is to raise awareness, and to this case series to be led for further investigations and to reach a consensus to routinely screen patients for adrenal insufficiency.

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