episodes continued. Latex allergy was considered but her latex IgE resulted <0.35 kU/L. Her mother expressed concern that her second and third reactions occurred after the initiation of a new bag of her previously tolerated elemental formula. The patient's elemental formula was sent to the Food Allergy Research and Resource Program at Nebraska Institute of Agriculture and Natural Resources to evaluate for possible milk contamination. This returned positive for milk presence at 200 parts/million. A new batch of the same formula was subsequently sent for evaluation and revealed no evidence of contamination. Given these findings, her reactions were attributed to milk contamination of the elemental formula. With initiation of the new batch of elemental formula, she did not have further episodes of anaphylaxis during her hospitalization or after discharge. On discharge follow-up, her IgE levels to alpha lactalbum, beta lactoglobulin, and casein were <0.35 kU/L whereas her IgE level to milk remained elevated (1.91 kU/L). The result of her skin prick test to milk was positive (9 mm wheal, 22 mm flare). Her tryptase level after discharge was 6.5 ng/mL. She continues to take her elemental formula by tube feed and avoids milk in all forms. A full food allergy workup can be referred to in Table 1.

Even though milk allergy is a common food allergy in the 0 to 3-year age group in the United States,[4] elucidating the cause for our patient's recurrent anaphylactic episodes proved challenging owing to many factors. First, the patient spent her entire life in the hospital and did not partake in solid food introduction in a standard fashion, making her risk for food allergy difficult to determine. Second, the eosinophil level after her episodes prompted concerns for other causes of anaphylaxis, such as drug allergy. Lastly, our patient was on an elemental formula so food allergy was not initially considered given that hypersensitivity reactions to elemental formulas are extremely rare.[5] Hidden food allergens are infrequently the cause of idiopathic anaphylaxis[6] and can be hard to find. Ultimately, evaluation of her elemental formula for cross contamination with milk revealed the cause of her anaphylaxis, illustrating hidden food allergens should be considered in the differential for patients who present with unexplained anaphylaxis.

Cross-contamination remains an area of concern for patients with food allergy as even trace amounts of food protein can trigger a reaction in sensitive patients.[7] A detailed history and thorough evaluation of possible environmental exposures, including hidden allergens and cross contamination, should be obtained in evaluation of anaphylactic reactions. Otherwise, there is risk of incorrectly labeling reactions as idiopathic, which is always a diagnosis of exclusion.

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Secondary adrenal suppression related to high doses of inhaled corticosteroids in patients with severe asthma

Check for updates

Asthma management guidelines recommend inhaled corticosteroids (ICS) as first-line therapy. Although long-time ICS use in patients with asthma has a more favorable safety profile than oral corticosteroids (OCS), it is still associated with adrenal suppression (AS) even in the absence of OCS use.[1,2] Subsequent secondary adrenal insufficiency (AI) has been reported. Still, there are limited data on the magnitude of the effect in patients with severe asthma treated with high ICS doses.[1]

We analyzed the effect of high ICS doses[3] on AS in patients with severe asthma when assessed by salivary cortisol as a screening tool. Salivary cortisol analysis is commercially available and accepted as a screening alternative owing to its substantial positive correlation with serum cortisol.[4-6] We included all patients referred to the severe asthma outpatient clinic with a confirmed diagnosis from December 2016 to December 2019. Severe asthma was established according to the definition proposed by the European Respiratory Society and the American Thoracic Society.[7] This study followed the Declaration of Helsinki ethical standards, and all participants signed informed consent. Collected data refer to the first appointment where a questionnaire regarding the following variables was completed: age, sex, body mass index, presence of rhinitis, atopy (assessed by skin prick tests for common aeroallergens), Asthma Control Test, total blood immunoglobulin E, serum eosinophils, fractional exhaled nitric oxide (FeNO) performed before

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spirometry using a Niox Vero, forced expiratory volume in 1 second (FEV_1) postbronchodilator, and type and dose of ICS and OCS bursts in the previous year. All patients on maintenance treatment with OCS at the time of the saliva collection or who reported bursts in the previous 6 weeks were excluded. The cortisol immunoassay was performed in the laboratory with fresh samples collected with a swab in the first 30 minutes after awakening at approximately 8 AM. Subjects were advised not to exercise, eat, drink, or brush their teeth before saliva collection.[4] They were asked to rinse their mouth with water a few minutes before and not use ICS or intranasal corticosteroids (INCS) for 12 hours before the sample collection. Reference values used for AI diagnosis according to the salivary cortisol were validated for this method.[8] An exploratory analysis with classical descriptive statistics was performed for all the variables. Categorical variables were reported as absolute frequencies and continuous variables with central tendency and dispersion measures (median, 25th and 75th percentiles—P25 and P75). Comparisons of proportions were tested with Pearson χ^2 or Fisher's exact test, as appropriate. The Mann-Whitney *U* test was used to evaluate the difference of medians. A significance level of .05 was considered significant.

A total of 28 subjects were included in the analysis. Of the subjects, 19 (67.8%) were children, and the female sex was predominant (64.3%). The median age was 15 years (P25-P75: 13-44.8), and most (89.3%) had allergic rhinitis. Atopy (sensitization to 1 or more airborne allergens) was present in 92.9% of the subjects, with dust mites being the most common (88.4%). The Asthma Control Test questionnaires revealed a median score of 18 (P25-P75: 15-22). In terms of lung function, subjects had a median FEV_1 of 87.4% (P25-P75: 69.2%-98.3%) and a postbronchodilator FEV_1 of 91.7% (P25-P75: 75.8%-100.7%) and a median FEV_1/forced vital capacity of 0.83 (P25-P75: 0.67-0.89) and a median measure of FeNO of 31 ppb (P25-P75: 16 ppb-48 ppb). In addition, 16 subjects (57.1%) had FeNO values greater than 20 ppb. Regarding ICS, 10 subjects (35.7%) used fluticasone furoate (200 μg/d) administered with dry powder inhaler (DPI-Ellipta), 10 (35.7%) fluticasone propionate (DPI-Dyskus, 500-1000 μg/d), and 8 (28.6%) budesonide (DPI-Turbohaler, 800 μg/d). The median total serum immunoglobulin E was 487 kU/L (P25-75: 241-917), and the median blood eosinophil count was 390 cells/μL (P25-75: 253-578). We identified 7 subjects (25%) with low morning salivary cortisol (<4.4 nmol/L); of those, 5 were children. Table 1 illustrates the comparison between subjects with normal or low morning salivary cortisol.

Overall, our sample included mainly pediatric subjects, predominantly of female sex, with allergic phenotype and type 2 inflammation pattern according to FeNO results. Evidence on the ICS effect on AS has been published,[1,2,9,10] suggesting it may occur at lower doses than previously thought. Although the clinical relevance of potential AI and the association with ICS is not clear, previous studies revealed that AS could present clinically as AI on sudden withdrawal of long-term therapy with ICS.[2]

We found a high rate (25%) of AS suspicion in subjects on high ICS doses even among children (26.3%). The AS cases found are not probably explained by corticosteroid bursts. Both groups had only 1 OCS prescription in the previous year, as found in Table 1.

Other studies[10] have found lower rates of AS in children, although different inclusion criteria and diagnostic methods might explain these results.

Salivary cortisol measurement method used does not replace serum cortisol in clinical diagnosis. Still, it has the advantage of being a noninvasive screening method for frequent monitoring of patients, especially children.

Our study has some limitations as it was conducted only in 1 center. We did not evaluate serum cortisol and adrenocorticotrophic hormone to compare with the salivary cortisol, nor did we consider in the analysis the current or past use of topical corticosteroids or INCS. Nevertheless, although it has been found that concomitant use of INCS and ICS can increase the rate of AS, as far as we know, most of the ICS safety evaluation studies also do not consider this cumulative effect.[9] We did not calculate the adequate sample size for statistical analyses, and so owing to the small sample size, differences might not have been detected.

Our study has several strengths, including the following: inclusion and evaluation of adults and children with severe asthma, especially in children, on whom information is scarce. Furthermore, all patients were followed carefully in a severe asthma clinic, specialists confirmed the diagnosis, and OCS use was equivalent in the groups. Our study suggests that both adults and children with severe asthma on ICS might have AS even without maintenance treatment with OCS. Although controlled trials are needed to verify the clinical significance, AS screening seems justifiable as it seems underestimated. AS should prompt additional considerations, such as biological treatment and monitoring of other adverse effects.

Table 1
Comparison Between Patients With Normal or Low Morning Salivary Cortisol

Parameter	Normal salivary cortisol (n = 21)	Low salivary cortisol(n = 7)	*P* value
Age (y), median (P25-P75)	14.0 (12.5-44.0)	15.0 (13.0-46.0)	.75
Adults, n (%)	7 (33.3)	2 (28.6)	>.99
Children, n (%)	14 (66.7)	5 (71.4)	
Female sex, %	61.9	71.4	>.99
BMI (kg/m^2), median (P25-P75)	19.5 (17.7-28.3)	25.3 (20.2-32.5)	.34
Rhinitis, %	90.5	85.7	>.99
Atopy, %	95.2	85.7	>.99
ACT, median (P25-P75)	19.0 (18.0-22.7)	15.0 (12.0-22.0)	.13
Total IgE (kU/L), median (P25-P75)	379 (226-883)	826 (301-1189)	.17
Blood eosinophils (cells/μL), median (P25-P75)	390 (255-550)	450 (130-590)	.91
FeNO (ppb), median (P25-P75)	29 (16-46)	34 (14-68)	.76
FEV_1 post-BD (%), median (P25-P75)	90.1 (79.4-96.3)	101.0 (54.6-117.9)	.41
Type of inhaled corticosteroid			.30
Budesonide (DPI, 800 μg/d)	6 (28.6)	2 (28.6)	
Fluticasone propionate (DPI, 500-1000 μg/d)	9 (42.8)	1 (14.3)	
Fluticasone furoate (DPI, 200 μg/d)	6 (28.6)	4 (57.1)	
OCS bursts previous year, median (P25-P75)	1 (0-2)	1 (0-3)	.67

Abbreviations: ACT, asthma control test; BD, bronchodilator; BMI, body mass index; DPI, dry powder inhaler; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; OCS, oral corticosteroid; P25, 25th percentile; P75, 75th percentile.

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Mode of onset and triggers of severe asthma

The severe asthma clinic perspective

A minority of people with asthma (5%-10%) develop a severe form of the disease that increases the risk of morbidity and mortality.[1] Severe asthma may be distinct from non severe asthma, or both may represent the 2 ends of 1 disease process.[2] Severe asthma can go unchecked for several years with consequent overreliance on oral corticosteroids (OCS) treatment that exposes patients to serious adverse effects.[3] To date, our knowledge of the mode of onset of severe asthma and its triggers remain limited. Understanding early events in severe asthma may lead to the development of tools of early detection and treatment.[4] Here, we studied the events leading up to severe asthma onset in patients referred to our tertiary severe asthma center. New patients referred from 2012 to 2017 were clinically characterized to confirm the diagnosis, assess the severity, and identify comorbidities.[5] Patients provided written consent for study inclusion (research and ethics committee reference: 09/H1206/120). Patients completed structured questionnaires and clinic interviews to ascertain the narrative of the mode of onset, timing and any observed triggers of their severe asthma. The onset of severe asthma was defined as the time of change from low to high symptom burden; use of low-dose to high-dose inhaled corticosteroids in conjunction with other controller therapy; and the use of 0 or 1 to more than 1 OCS course per annum. Themes of events leading up to severe asthma onset were clustered according to the type of the observed insult or trigger, mode of onset (rapid vs gradual), and whether severe asthma started as a mild disease or severe at onset de novo. Insults or triggers were divided into infective and noninfective types. A pragmatic cutoff period of 6 months was used to demarcate rapid from gradual-onset forms.

A total of 148 patients (mean age, 45 years [range, 16-94], 70% women) with a confirmed diagnosis of severe asthma were included in the analysis. The median body mass index was 31 kg/m^2 (interquartile range, 26-37). The mean forced expiratory volume in 1 second (FEV_1) was 2.1 L (±0.77) (FEV_1% predicted, 70.3 ± 22.4) and the mean FEV_1 to forced vital capacity ratio was 0.65 (±0.15).[3] The median age at onset of asthma was 13.5 years (interquartile range, 4-30). Most patients (82.4%) had early-onset asthma (<40 years of age), and 17.6% had late-onset asthma (≥40 years). The median duration of time from onset of asthma to the onset of severe disease was 14 years (range, 4-28). The observed modes of onset and triggers of severe asthma are presented in Table 1. The change to severe disease was gradual in 72 of 148 (48.7%) cases and rapid in 76 of 148 (51.3%). In the rapid group, the triggers were infective in 45 out of 76 (59.2%) and noninfective in 31 out of 76 (40.8%) cases. The infective events included 20 cases of lower respiratory tract infection, 7 cases of pneumonia, 1 croup, 1 rhinosinusitis, 1 influenza, and unspecified in 15 cases. The noninfective triggers included 6 cases of acute inhalation accidents (2 colophonies, 1 vacuum cleaner, 1 smoke inhalation from factory fire, 1 diesel fume, and 1 horsehair), 1 case of ingestion of a nonsteroidal anti-inflammatory drug, and 1 female patient who developed severe asthma at the onset of puberty. In 19 cases, severe asthma developed after an acute life-threatening asthma exacerbation of an undetermined trigger on a background of nonsevere asthma. Asthma commenced as severe from the onset de novo in 4 cases. We observed no significant difference between the groups in terms of lung function, type 2 biomarkers, or exacerbation frequency. Factors contributing to gradual progression onto severe asthma were not evident in our study; but previously, poor asthma control, ongoing exposure to environmental triggers, frequent exacerbations and airway remodeling have been reported to cause progression to severe disease.[6] Poor asthma control is still prevalent despite the availability of effective treatments with an observed persistent gap between guideline-recommended control goals and real-life experience.[7] Asthma control is also worsened by comorbidities.[8] In our study, 85% of cases had at least 1 comorbidity, and a third had 4 or more comorbidities (data not provided). Comorbidities such as obesity, sleep apnea, and corticosteroid insensitivity often coexist and are linked to the frequent use of OCS (56% of patients in our study were on OCS maintenance).

Acute infective events coincided with severe asthma onset in one-third of the cases in our study. The retrospective design of this study did not allow for delineation of the causative microorganisms, but we broadly observed a range of acute viral and bacterial infections of the upper and lower respiratory tract. Patients with asthma are highly susceptible to viral and bacterial infections and mechanisms

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