Adrenal reserve in acute exacerbation of non-cystic fibrosis bronchiectasis

Sir,

Bronchiectasis (BXSIS) is characterized by non-reversible airway dilatation due to a variety of respiratory insults, and a few evidence-based medical therapies exist for the treatment of non-cystic fibrosis bronchiectasis. Acute exacerbations of bronchiectasis (AE-BXSIS) result in episodic worsening of lung function and symptoms. Frequent exacerbations may accelerate decline in lung function and increase in mortality. Goals of therapy in stable bronchiectasis include reduction in exacerbations and improvement in quality of life (QOL).

Patients with AE-BXSIS often experience increasing fatigue and expectoration, which significantly impair QOL and work capacity. Increasing evidence suggests frequent adrenal insufficiency in stable bronchiectasis and correlates with symptoms and QOL as measured by the St. George’s Respiratory Questionnaire (SGRQ). In a previous study, we found a similar prevalence of suppressed adrenal responses in patients from south India with stable bronchiectasis. Little is known about adrenal responses during AE-BXSIS and relationship of these to longitudinal responses in stable state; also, the correlation of these responses with fatigue and QOL is unknown. We, therefore, conducted a pilot observational study at the St. John’s Medical College Hospital, Bengaluru, India, between April 2009 and February 2012 to evaluate adrenal responses to 1 µg cosynotropin during AE-BXSIS and six weeks after resolution of AE-BXSIS. The study was approved by the Institutional Ethics committee. The inclusion and exclusion criteria for bronchiectasis, study setting and methodology, reason for choice of 1 µg test and cut offs (≤17.5 µg/dl post-stimulation) have been described previously. The aetiology of bronchiectasis was made based on clinical history and appropriate use of testing as per guidelines. AE-BXSIS was defined as subjective and persistent (≥24 h) deterioration in at least four of the following nine parameters: fever (temperature greater than 37.5°C), cough, dyspnoea, haemoptysis, sputum purulence or volume, chest pain, respiratory signs on examination, radiographic signs and systemic symptoms. The details of the enrolled patients are provided in Table I. Five patients (25%) failed to mount a positive response and fulfilled the criteria for adrenal insufficiency (post-stimulation cortisol ≤17.5 µg/dl). Basal cortisol values were not significantly different between patients with and without impaired adrenal reserve (IAR); 30-min post-stimulation values were significantly lower in patients with adrenal insufficiency (P=0.001). Tuberculosis as a cause of bronchiectasis was significantly associated with IAR [P<0.01 (Fisher’s Exact test) Table II].

Data on repeat testing of 1 µg synacthen was available in 11 of 20 patients (Figure). While there was a clear trend towards an increase in both basal (mean difference=2.59, P=0.14) and 30-minute cortisol values (mean difference=1.94, P=0.32), these values did not reach statistical significance. Using a cut-off of 17.5 µg/dl for IAR, 8 of 11 (72.7%) patients were classified the same way on repeat 1 µg synacthen testing. Two (18%) patients who were classified as normal during exacerbation had value suggestive of impaired adrenal reserve when re-tested during stable state and one had normal testing during stable state but failed to show incremental response during an exacerbation.

The lack of association of basal values and AE-BXSIS is possibly because of heightened stress responses due to an exacerbation; however, a clear separation existed in 30-min stimulation values and this persisted after resolution of an exacerbation. A low 30-min cortisol response with active tuberculosis has been well documented. Our previous study on stable bronchiectasis showed a correlation between SGRQ...
Table I. Characteristics of patients with acute exacerbation of bronchiectasis (N=20)

| Parameter                                      | Mean ± standard deviation or number (percentage) |
|------------------------------------------------|-------------------------------------------------|
| Gender                                         | Male 15 (75); female 5 (25)                     |
| Age (yr)                                       | 43.25 ± 16.75                                   |
| Symptom duration (yr)                         | 14.76 ± 9.93                                    |
| Sputum amount per day (ml/day)                | 42.4 ± 9.93                                     |
| Number of days with purulent sputum (N=12)*     | 12 ±7.8 days per month                          |
| Smoking history                               | 18 (90) never smokers; 2 (10) former smokers    |
| Body mass index (kg/m²)                       | 20.11 ± 3.91                                    |
| Nausea and/or vomiting                         | 3 (15)                                          |
| Fatigue                                       | 5 (25)                                          |
| Weight loss                                    | 2 (10)                                          |
| Postural drop in blood pressure (mm Hg)        | 1 (5)                                           |
| Bronchiectasis aetiology                      | Idiopathic 8 (40); Post-tuberculosis 6 (30); Post-necrotizing pulmonary infections 2 (10); Others 4 (20) |
| Bronchiectasis extent                         |                                                 |
| Severe bronchiectasis (≥ grade 3)             | 11 (55)                                         |
| Bronchiectasis severity score#                | 103.25 ± 41.07                                  |
| Pulmonary artery hypertension                  | 5 (25)                                          |
| FEV₁ (N=19)                                    | 1.37±0.48 l; 45.27 ± 12.80 per cent predicted   |
| FVC (l) (N=19)                                 | 1.85±0.63 l; 51.22 ± 15.17 per cent predicted   |
| Inhaled corticosteroids use                    | 12 (60)                                         |
| Six-minute walk distance (meters)              | 443.54±161.31                                   |
| SGRQ                                           |                                                 |
| Symptoms domain                                | 66.10±19.12                                     |
| Activity domain                                | 68.88±28.06                                     |
| Impact domain                                  | 62.05±25.33                                     |
| Total                                          | 64.80±22.23                                     |
| Adrenal responses                              |                                                 |
| Basal cortisol (µg/dl)                         | 13.36 ± 2.94                                    |
| 30 min stimulated cortisol (µg/dl)             | 19.5 ± 3.38                                     |
| 1 µg synacthen test failures$                 | 5 (25)                                          |

*Defined as 30-min post-1 µg synacthen stimulation cortisol value of ≤ 17.5 µg/dl
SGRQ, St. George’s Respiratory Questionnaire; FEV₁, forced expiratory vital capacity in 1 sec; FVC, forced vital capacity
*Data available only for 12 of the 20 patients
$Ref. 10
scores and IAR, but we did not find a correlation with post-tuberculosis aetiology and IAR in that study\(^7\). Repeat testing was performed in only 11 patients. Most of the patients remained in the same class, suggesting that the IAR might be a persistent abnormality rather than being specific for the acute phase. It is well known that there is significant variability on repeat testing in adrenal stimulation tests\(^1\). Two patients who were classified as normal during exacerbation were diagnosed to have IAR on repeat examination.

Hypothalamo-pituitary-adrenal (HPA)-axis dysfunction could be a part of acute and/or chronic inflammatory disease because of its obvious therapeutic implications. Larger longitudinal studies with repeated examination of adrenal function in bronchiectasis both during acute exacerbation and in the stable phase are required for a better understanding of the contribution of HPA-axis to symptomatology, quality of life and mortality in bronchiectasis.

Conflicts of Interest: None.
Acknowledgment

Authors thank Dr P.J. Jones, for kindly providing permission to use the St. George’s Respiratory Questionnaire in English and local languages.

Srinivas Rajagopala¹,*
Anantharaman Ramakrishnan¹,
Anushree Chakraborty²,
Ganapathi Bantwal¹,
Uma Devaraj² & George D’Souza²
Departments of ¹Endocrinology,
²Pulmonary Medicine,
St John’s Medical College Hospital,
Sarjapur Road, Bengaluru 560 034, Karnataka &
³Department of Medicine,
Jawaharlal Nehru Institute of Postgraduate Medical Education & Research,
Dhanvantri Nagar, Górimedu,
Puducherry 605 006, India
*For correspondence
visitsrinivasan@gmail.com

References

1. Pasteur MC, Bilton D, Hill AT; British Thoracic Society Non-CF Bronchiectasis Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. Thorax 2010; 65 : 577.
2. O’Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group. Chest 1998; 113 : 1329-34.
3. O'Donnell AE. Bronchiectasis. Chest 2008; 134 : 815-23.
4. Martinez-Garcia MA, Soler-Cataluna JJ, Perpina-Tordera M, Roman-Sanchez P, Soriano J. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. Chest 2007; 132 : 1565-72.
5. Gompertz S, O’Brien C, Bayley DL, Hill SL, Stockley RA. Changes in bronchial inflammation during acute exacerbations of chronic bronchitis. Eur Respir J 2001; 17 : 1112-9.
6. Holme J, Tomlinson JW, Stockley RA, Stewart PM, Barlow N, Sullivan AL. Adrenal suppression in bronchiectasis and the impact of inhaled corticosteroids. Eur Respir J 2008; 32 : 1047-52.
7. Rajagopala S, Ramakrishnan A, Bantwal G, Devaraj U, Swamy S, Ayyar SV, et al. Adrenal insufficiency in patients...
with stable non-cystic fibrosis bronchiectasis. Indian J Med Res 2014; 139 : 393-401.

8. Pasteur MC, Helliwell SM, Houghton SJ, Webb SC, Fowler JE, Coulden RA, et al. An investigation into causative factors in patients with bronchiectasis. Am J Respir Crit Care Med 2000; 162 : 1277-84.

9. Barker AF, Bardana EJ, Jr. Bronchiectasis: update of an orphan disease. Am Rev Respir Dis 1988; 137 : 969-78.

10. Lynch DA, Newell J, Hele V, Dyer D, Corkery K, Fox NL, et al. Correlation of CT findings with clinical evaluations in 261 patients with symptomatic bronchiectasis. AJR Am J Roentgenol 1999; 173 : 53-8.

11. Casanova-Cardiel LJ, Flores-Barrientos OI, Schabib-Hany M, Miranda-Ruiz R, Castanon-Gonzalez JA. Cosyntropin test in severe active tuberculosis. Cir Cir 2008; 76 : 305-9.

12. Prasad GA, Sharma SK, Mohan A, Gupta N, Bajaj S, Saha PK, et al. Adrenocortical reserve and morphology in tuberculosis. Indian J Chest Dis Allied Sci 2000; 42 : 83-93.

13. Azziz R, Bradley E Jr, Huth J, Boots LR, Parker CR Jr, Zacur HA. Acute adrenocorticotropic (ACTH) adrenal stimulation in eumenorrheic women: reproducibility and effect of ACTH dose, subject weight, and sampling time. J Clin Endocrinol Metab 1990; 70 : 1273-9.