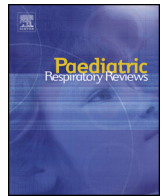




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Severe pulmonary exacerbation in cystic fibrosis caused by cat allergy

Rishi Pabary^{1,2}

¹ Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London

² Imperial College, London

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SUMMARY

This paper describes a preschool child who had persistent symptoms suggestive of significant cystic fibrosis lung disease over a period of eighteen months following first isolation of *Pseudomonas aeruginosa*. Despite vigorous anti-infective treatment and extensive investigations seeking undetected infection, improvement only occurred once severe cat allergy was diagnosed and cats were removed from the household. Whilst infection is the most common cause of respiratory exacerbations in cystic fibrosis, this article serves as a reminder that it is important to consider non-infective pathologies when the response to anti-infective treatment is unexpectedly poor.

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INTRODUCTION

Pulmonary exacerbations in cystic fibrosis (CF) are common, with preschool children experiencing an average of 3.66 exacerbations per year, of which approximately 20% will require hospital admission [1]. There are currently no standard criteria by which exacerbations are diagnosed [2] and, given the difficulties of performing spirometry in preschool children [3], objective measurements of lung function in this age group are lacking. Furthermore, as children are often unable to expectorate sputum, oropharyngeal cultures are used as an alternative but have poor sensitivity and do not reliably predict the presence of pathogens, in particular *Pseudomonas aeruginosa* (Pa), in the lower airways [4]. Diagnosis of pulmonary exacerbations in children therefore relies on clinical signs and symptoms such as increased cough and crackles on chest auscultation [5] which are non-specific and can thus be misleading. This paper describes a patient who presented with symptoms suggestive of an infective exacerbation whose symptoms were in fact the result of allergic airway disease, which is a common fellow traveller in CF [6].

CASE REPORT

A two-year-old boy diagnosed with CF ($\Delta F508/3905\text{insT}$) in the newborn period following a bowel perforation on day three of life, presented with a first growth of Pa on cough swab in January 2011 and was initially treated with oral ciprofloxacin and nebulised colistin. Due to ongoing symptoms, he then received a two-week

course of intravenous (IV) antibiotics and was kept on nebulised therapy. Subsequent oropharyngeal cultures grew Pa (non-mucoid) and he was treated with further oral antibiotics. He had recurrence of a moist cough in February 2012 (aged three years) and was treated with intravenous antibiotics; bacterial cultures were negative but there was minimal improvement in symptoms. He had a persistent cough until May 2012 and parents stated that “he had not been right for months” and he was therefore readmitted in June 2012 for further intravenous antibiotics. He underwent flexible bronchoscopy as there was no improvement after two weeks of IV ceftazidime and tobramycin and had a third week of IV colistin and meropenem. Bronchoalveolar lavage grew only scanty *Aspergillus fumigatus*. The IgE concentration was 114 IU/ml and specific IgE to *Aspergillus fumigatus* was 0.36 IU/ml. Due to a relative lack of improvement and despite these findings, he was commenced on itraconazole and a five-day course of oral prednisolone prior to discharge.

Symptoms improved for a brief time but when he was seen again in outpatients in August 2012 there had been a recurrence of his cough, which was worst at night and first thing in the morning. It was felt that he may be having a reaction to nebulised colistin, so pre-dosing with salbutamol was commenced with some improvement. The history was subsequently revisited and it transpired that there were two cats in the house, which had been present since the child was born, but no family history of atopy and no smoking contacts. A repeat IgE concentration was 239 IU/ml but the specific IgE to cat dander was grossly elevated at 57 IU/ml. Specific IgE to dog dander, grass and tree pollen were also moderately raised. Cats were therefore removed from the house and there was significant improvement in symptoms over the following four months. Ventilation scan in February 2013 was unremarkable and he

E-mail address: R.Pabary@rbht.nhs.uk.

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was entirely asymptomatic. Itraconazole was stopped and the child has remained well; he has had no bacterial growths for almost two years and there is a plan to stop nebulised colistin if he remains symptom-free.

In this case, persistent cough during 2012 was not necessarily indicative of an infective exacerbation of CF but, because of the unreliability of oropharyngeal culture and previous growths of *Pa.*, negative cough swabs were considered a poor indicator of true *Pa.* status. Spirometry may have revealed an obstructive picture (airway hyper-responsiveness with a relative reduction in FEV₁ compared to FVC) but could not be performed given the age of this child and in any case this picture is not uncommon in CF without concomitant asthma. In retrospect, the fact that symptoms improved during a family holiday to Antigua and after starting oral steroids are in keeping with allergic sensitisation. This highlights the importance of revisiting the history in chronic conditions such as CF where patients are seen regularly and are therefore less likely to be asked about social circumstances during consultations when compared with patients who have been newly referred.

DISCUSSION

The diagnosis of asthma in preschool children is complicated and is particularly difficult in patients with CF [7]. “CF asthma” is the term applied to patients who have episodes of airway obstruction reversed by bronchodilators, a family history of asthma or, as in our patient, evidence of atopy [8] with prevalence of around 14% in preschool children [9]. The incidence of allergy (hypersensitivity) and asthma in children with CF has been shown to be higher than in the general population [8,10] although the pathophysiology may be different to that of non-CF asthma, as demonstrated by different responses to inhaled methacholine and histamine [11] and the fact that the major allergic responses are to *Aspergillus fumigatus* and other moulds as opposed to the more usual aeroallergens such as house dust mite [12]. The basic defect in CFTR may itself predispose to an asthmatic phenotype, as suggested by the finding of increased incidence in heterozygotes with one mutation [13], although the evidence for this remains equivocal [14,15]. Airway remodelling and increased smooth muscle mass, reminiscent of that seen in non-CF asthma, has been demonstrated in CF [16,17] but it remains unclear whether this is due to mutations in CFTR (which is expressed in smooth muscle [18]) or secondary to infection and chronic inflammation. Regardless of the purported differences in pathophysiology, diagnosis and management of both CF and non-CF asthma is similar [7] and beyond the scope of this article.

Elevated IgE antibodies to cat dander are present in 62% of children with asthma [19] although the effect of exposure in early life remains unclear [20]. The cat dander protein Fel d 1 is the major cause of allergic human responses to cat [21] but does not directly activate the human innate immune system [22]. It has recently been demonstrated that Fel d 1 is only recognised by toll-like receptors (TLR4) when bound to lipopolysaccharide (LPS), a component of the cell membrane of gram-negative bacteria such as *Pa.*, and that immune responses are only triggered in the presence of a third protein (MD2) which binds LPS to TLR4. This may explain why a higher incidence of allergy, previously attributed to increased antigenic effect secondary to retention in thick secretions and action on already damaged airway epithelium, has been noted in CF patients with *Pa.* infection [23]. Counter to this theory is the finding that sensitisation to cat dander on skin prick testing is only 16% in allergic children with CF, compared to 58% in those without CF [10], suggesting that the presence of LPS in the airway does not itself increase the risk of allergy. Although the precise allergic mechanism of Fel d 1 is becoming clearer, the only current treatments for cat allergy are antihistamines, which vary in

effectiveness between individuals, cat washing (only transiently beneficial [24]) or animal avoidance. Whilst avoidance was successful in this case, it is not always the case due to passive transfer of allergens between environments [25], the ability of cat allergens to stay airborne for long periods of time [20] and the fact that even tiny amounts can elicit a chronic airway inflammatory response in sensitised individuals [26]. When advocating animal removal it should be noted that symptoms may not improve immediately as cat allergen levels can persist for up to 6 months [27] and, for this reason, if it is not possible to remove an animal from the home we advise strict segregation away from areas in which the child sleeps. Phase III clinical trials are currently underway to investigate the potential of TLR4 antagonists as an alternative therapy but, as there at least four other major cat allergens [21,28] which may induce symptoms by other mechanisms, this approach is unlikely to be a panacea.

CONFLICT OF INTEREST

The author has no conflict of interest to report.

References

- [1] Byrnes CA, Vidmar S, Cheney JL, et al. Prospective evaluation of respiratory exacerbations in children with cystic fibrosis from newborn screening to 5 years of age. *Thorax* 2013;**68**(7):643–51. Epub 2013/01/25.
- [2] Smyth A, Elborn JS. Exacerbations in cystic fibrosis: 3–Management. *Thorax* 2008;**63**(2):180–4. Epub 2008/02/01.
- [3] Beydon N, Davis SD, Lombardi E, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *American Journal of Respiratory and Critical Care Medicine* 2007;**175**(12):1304–45. Epub 2007/06/05.
- [4] Tramper-Stranders GA, van der Ent CK, Wolfs TF. Detection of *Pseudomonas aeruginosa* in patients with cystic fibrosis. *Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society* 2005;**4**(Suppl 2):37–43. Epub 2005/06/18.
- [5] Rabin HR, Butler SM, Wohl ME, et al. Pulmonary exacerbations in cystic fibrosis. *Pediatric Pulmonology* 2004;**37**(5):400–6. Epub 2004/04/20.
- [6] McCuaig S, Martin JG. How the airway smooth muscle in cystic fibrosis reacts in proinflammatory conditions: implications for airway hyper-responsiveness and asthma in cystic fibrosis. *The Lancet Respiratory Medicine* 2013;**1**(2):137–47.
- [7] Balfour-Lynn IM, Elborn JS. CF asthma”: what is it and what do we do about it? *Thorax* 2002;**57**(8):742–8.
- [8] Morgan WJ, Butler SM, Johnson CA, et al. Epidemiologic study of cystic fibrosis: design and implementation of a prospective, multicenter, observational study of patients with cystic fibrosis in the U.S. and Canada. *Pediatric Pulmonology* 1999;**28**(4):231–41. Epub 1999/09/25.
- [9] Koch C, McKenzie SG, Kaplowitz H, et al. International practice patterns by age and severity of lung disease in cystic fibrosis: data from the Epidemiologic Registry of Cystic Fibrosis (ERCF). *Pediatric Pulmonology* 1997;**24**(2):147–54. discussion 59–61. Epub 1997/08/01.
- [10] Warner JO, Taylor BW, Norman AP, Southall JF. Association of cystic fibrosis with allergy. *Archives of Disease in Childhood* 1976;**51**(7):507–11. Epub 1976/07/01.
- [11] Mitchell I, Corey M, Woenne R, Krastins IRB, Levison H. Bronchial hyperreactivity in cystic fibrosis and asthma. *The Journal of Pediatrics* 1978;**93**(5):744–8.
- [12] Warner JO, Kilburn SA. Cystic fibrosis and allergy. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology. 1996; 7(9 Suppl):67–9. Epub 1996/01/01.
- [13] Tzetzis M, Efthymiadou A, Strofalis S, et al. CFTR gene mutations—including three novel nucleotide substitutions—and haplotype background in patients with asthma, disseminated bronchiectasis and chronic obstructive pulmonary disease. *Hum Genet* 2001;**108**(3):216–21. Epub 2001/05/17.
- [14] Dahl M, Tybjaerg-Hansen A, Lange P, Nordestgaard BG. DeltaF508 heterozygosity in cystic fibrosis and susceptibility to asthma. *Lancet* 1998;**351**(9120):1911–3. Epub 1998/07/08.
- [15] Schroeder SA, Gaughan DM, Swift M. Protection against bronchial asthma by CFTR delta F508 mutation: a heterozygote advantage in cystic fibrosis. *Nature Medicine* 1995;**1**(7):703–5. Epub 1995/07/01.
- [16] Regamey N, Ochs M, Hilliard TN, et al. Increased airway smooth muscle mass in children with asthma, cystic fibrosis, and non-cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2008;**177**(8):837–43. Epub 2008/01/26.
- [17] Hays SR, Ferrando RE, Carter R, Wong HH, Woodruff PG. Structural changes to airway smooth muscle in cystic fibrosis. *Thorax* 2005;**60**(3):226–8. Epub 2005/03/03.
- [18] Michoud MC, Robert R, Hassan M, et al. Role of the cystic fibrosis transmembrane conductance channel in human airway smooth muscle. *American Journal of Respiratory Cell and Molecular Biology* 2009;**40**(2):217–22. Epub 2008/09/02.

- [19] Ingram JM, Sporik R, Rose G, Honsinger R, Chapman MD, Platts-Mills TA. Quantitative assessment of exposure to dog (Can f 1) and cat (Fel d 1) allergens: relation to sensitization and asthma among children living in Los Alamos, New Mexico. *The Journal of Allergy and Clinical Immunology* 1995;**96**(4):449–56. Epub 1995/10/01.
- [20] Chapman MD, Wood RA. The role and remediation of animal allergens in allergic diseases. *The Journal of Allergy and Clinical Immunology* 2001;**107**(3 Suppl):S414–21. Epub 2001/03/10.
- [21] Lowenstein H, Lind P, Weeke B. Identification and clinical significance of allergenic molecules of cat origin. Part of the DAS 76 Study. *Allergy* 1985;**40**(6):430–41. Epub 1985/08/01.
- [22] Herre J, Gronlund H, Brooks H, et al. Allergens as immunomodulatory proteins: the cat dander protein Fel d 1 enhances TLR activation by lipid ligands. *J Immunol* 2013;**191**(4):1529–35. Epub 2013/07/24.
- [23] Pitcher-Wilmott RW, Levinsky RJ, Gordon I, Turner MW, Matthew DJ. Pseudomonas infection, allergy, and cystic fibrosis. *Archives of Disease in Childhood* 1982;**57**(8):582–6. Epub 1982/08/01.
- [24] Avner DB, Perzanowski MS, Platts-Mills TA, Woodfolk JA. Evaluation of different techniques for washing cats: quantitation of allergen removed from the cat and the effect on airborne Fel d 1. *The Journal of Allergy and Clinical Immunology* 1997;**100**(3):307–12. Epub 1997/10/06.
- [25] Almqvist C, Larsson PH, Egmar AC, Hedren M, Malmberg P, Wickman M. School as a risk environment for children allergic to cats and a site for transfer of cat allergen to homes. *The Journal of Allergy and Clinical Immunology* 1999;**103**(6):1012–7. Epub 1999/06/09.
- [26] Bollinger ME, Eggleston PA, Flanagan E, Wood RA. Cat antigen in homes with and without cats may induce allergic symptoms. *The Journal of Allergy and Clinical Immunology* 1996;**97**(4):907–14. Epub 1996/04/01.
- [27] Wood RA, Chapman MD, Adkinson Jr NF, Eggleston PA. The effect of cat removal on allergen content in household-dust samples. *The Journal of Allergy and Clinical Immunology* 1989;**83**(4):730–4. Epub 1989/04/01.
- [28] Adedoyin J, Gronlund H, Oman H, Johansson SG, van Hage M. Cat IgA, representative of new carbohydrate cross-reactive allergens. *The Journal of Allergy and Clinical Immunology* 2007;**119**(3):640–5. Epub 2007/03/06.