

F. VÍLCHEZ-SÁNCHEZ¹, J. DOMÍNGUEZ-ORTEGA^{1,2}, M. GONZÁLEZ MUÑOZ³, D. LOLI-AUSEJO¹, R. HEREDIA-REVUELTO¹, A. FIANDOR ROMÁN¹, S. QUIRCE^{1,2}

Two case reports of delayed-allergic reactions to clindamycin confirmed with a positive lymphocyte transformation test

¹Department of Allergy, La Paz University Hospital, Institute for Health Research (IdiPaz), Madrid, Spain

²CIBER de Enfermedades Respiratorias, Ciberes, Madrid, Spain

³Department of Immunology, La Paz University Hospital, Madrid, Spain

KEY WORDS

clindamycin; allergy; delayed reaction; lymphocyte transformation test; diagnosis

Corresponding author

Francisca Vílchez-Sánchez
Department of Allergy,
La Paz University Hospital
Paseo de la Castellana, 261
28046 Madrid, Spain
E-mail: franvilsan@gmail.com

Doi

10.23822/EurAnnACI.1764-1489.117

Introduction

Clindamycin is a lincosamide antibiotic that binds exclusively to the 50s subunit of bacterial ribosomes and suppresses intracellular protein synthesis. It is widely used in the prophylaxis and treatment of infections due to its broad spectrum of antimicrobial activity. Hypersensitivity to clindamycin seems to be not very common (less than 1% of drug-allergic reactions) (1), with mostly non-immediate or delayed ones: drug rash with eosinophilia and systemic symptoms (DRESS) (2), symmetric drug-related intertriginous and flexural exanthema (SDRIFE) (3), drug-induced hypersensitivity syndrome (DIHS) (4), generalized maculopapular exanthema (5), anaphylaxis (6) and acute generalized (7) and localised exanthematous pustulosis (8) have been described.

The diagnostic approach includes a detailed medical history, clinical examination, and skin testing and/or oral challenge with

Summary

Clindamycin is widely used in the prophylaxis and treatment of infections due to its broad spectrum of antimicrobial activity. Hypersensitivity to clindamycin seems to be not very common (less than 1% of drug-allergic reactions) and it mostly appears as delayed T-cell mediated. For the diagnosis, skin testing is considered to be highly sensitive and rather safe, but cutaneous and systemic reactions have been described. Provocation test is considered the “gold standard”. However, it includes the possibility of severe reactions. We reported two cases of delayed allergic reaction to clindamycin confirmed with a positive lymphocyte transformation test, showing this in vitro test like a promising diagnostic method because of its usefulness and safety.

clindamycin. Lymphocyte transformation test (LTT) in general has been shown to be more sensitive than skin testing for non-immediate reactions diagnosis (9,10,11), although there are only few studies that analyze the LTT in allergy to betalactams or quinolones, so its diagnostic value for other antibiotics remains uncertain (12).

We present two different cases of delayed allergic reaction to clindamycin with maculopapular exanthema in which LTT confirmed clindamycin as the culprit agent.

Clinical cases

Case 1. A 64-year-old woman who came to the allergy department from the emergency department to be studied for a possible allergy to clindamycin. She denied any past history of urticarial episodes or adverse reactions to the ingestion of food or medication. In September 2013 she took clindamycin for a

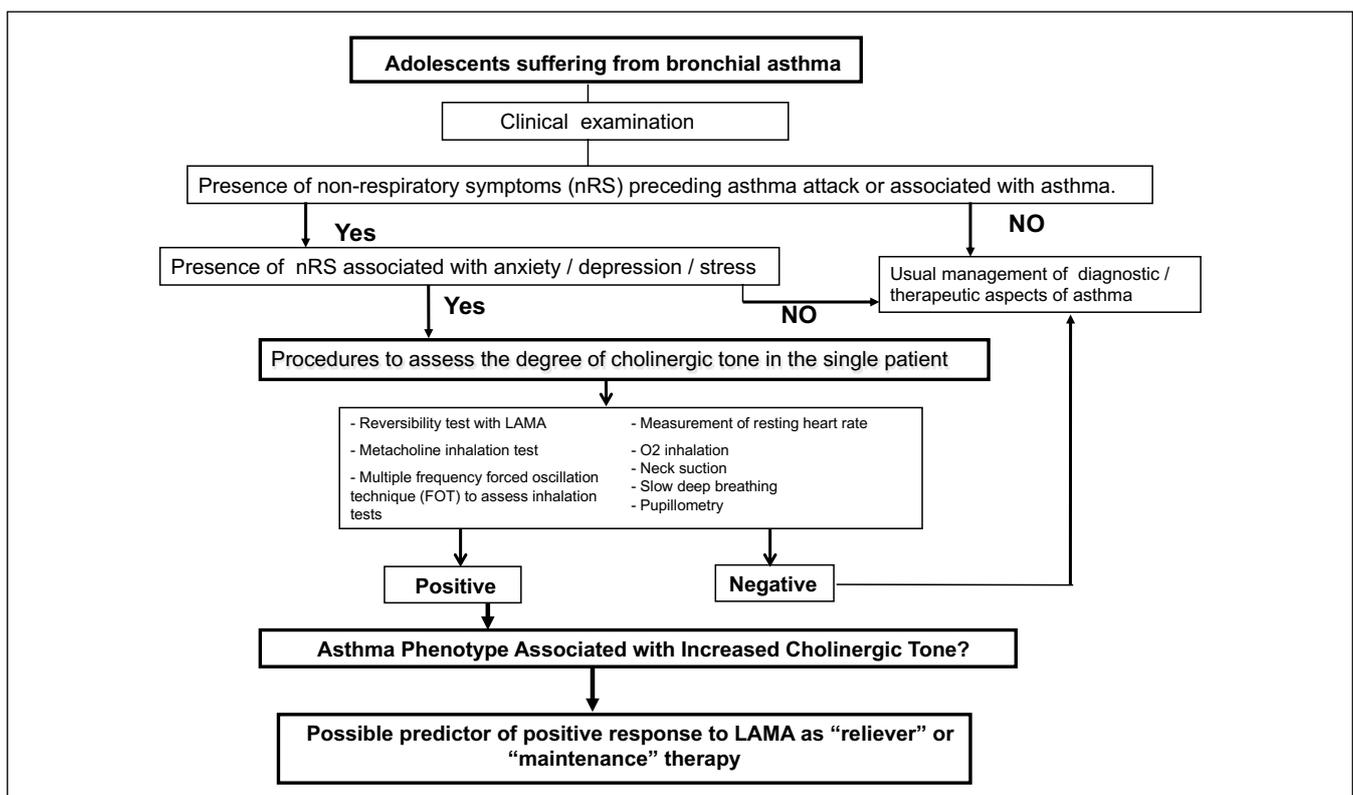
herence to their medical regimens, poor symptom control and poor treatment outcomes. Asthma during adolescence impairs health-related quality of life, especially in case of uncontrolled symptoms (2). It has been demonstrated that parental stress and air pollution were synergistically associated with increased childhood asthma, indicating a common biological effect of parental stress and air pollution during both prenatal and postnatal periods. Therefore, we would like to suggest some potential mechanisms to explain the correlation between stress/anxiety and asthma in adolescents. We have previously shown that about 63% of asthmatic patients reported the usual appearance of at least one non-respiratory symptom (n-RS) before an asthma attack (3). Anxiety and, to a lesser extent, depression, represented the most common n-RSs in our study, suggesting that both anxiety and depression may have a possible role in the development and trigger of an asthma attack. Several studies have shown that psychological stress may enhance bronchial hyperreactivity through different mechanisms, such as mast cell activation, mediator release, inflammation, impairment of respiratory tolerance. Moreover, Ritz. et al. (4) reported a significant correlation between psycho-social stress and stimulation of the cholinergic system, resulting in an increased airway resistance. Visual stimulations

(i.e. scenes from educational surgery) can rapidly induce (after 1-2 minutes) vagal-mediated responses associated with airway resistance increase. Therefore, we suggest that attention should be focused on the potential role of the parasympathetic system as a trigger of bronchial obstruction in asthmatic adolescents reporting the usual onset of cholinergic-related n-RSs (i.e. stress and/or anxiety) before an asthma attack. Indirectly, the results of our study (5) confirm a significant role of the cholinergic pathway in the enrolled asthmatic subject.

The vagal hyperactivity induced by anxiety and stress in asthmatics also represents the basis of important considerations by a therapeutic point of view, such as the use of anticholinergic agents. Considering this background, we suggest the need of an adequate phenotyping of asthmatic adolescents who could exhibit an increased basal cholinergic tone (6,7). The effect of oxygen and methacholine inhalation, neck suction, slow deep breathing assessed by multiple frequency forced oscillation technique (FOT), as well as measurement of resting heart rate and pupillometry, represent the most effective methods for evaluating the level of vagal tone (8) (**figure 1**).

According to our previous study (5), a simple question exploring the presence of vagal-related n-RSs during the collection of an-

Figure 1 - Suggested flow-chart for a better phenotyping of asthmatic adolescents suffering from anxiety/depression.



amnesic data could help to identify asthmatics with imbalance between sympathetic and parasympathetic systems who could benefit of further diagnostic evaluation of vagal tone. Since the degree of cholinergic tone is likely to be different among asthmatics, we believe it is not possible to rule out that the effectiveness of anticholinergic agents such as tiotropium could be greater in patients with an increased degree of cholinergic tone (9). This possible increased responsiveness to tiotropium may be usefully exploited also in the event of poor efficacy or occurrence of adverse events with the use of long-acting β_2 agonists (LABAs) (**figure 1**).

In conclusion, the currently available literature indicates that anxiety and related psychological disorders should be considered as mechanisms that might trigger the airway inflammation, the onset of asthma attacks, and the severity of respiratory symptoms. We concur with Licari et al (1) and others (10) that

adequate educational programs should be planned for those asthmatic patients suffering from psychological disorders (both in adults and minors). We believe that this approach requires a peculiar attention in adolescents, in order to obtain a better control of respiratory symptoms in the short term, a delay in asthma progression, and a reduced airway remodeling in the long term.

Acknowledgements

We thank the biologist dr. Mariagrazia Iengo and Francesca Lavaca for technical assistance in the preparation of this manuscript.

Conflict of interests

The authors declare that they have no conflict of interest

References

- Licari A, Ciprandi R, Marseglia G, Ciprandi G. Anxiety/depression changes are associated with improved asthma control perception in asthmatic adolescents after adequate management. *Eur Ann Allergy Clin Immunol* 2019; 51:190-192.
- Jonsson M, Bergstrom A, Egmar AC, Hedlin G, Lind T, Kull I. Asthma during adolescence impairs health-related quality of life. *J Allergy Clin Immunol Pract* 2016; 4:144-146.
- Liccardi G, Baldi G, Berra A, Carpentieri E, Cutajar M, D'Amato M, Del Donno M, Del Prato B, Folletti I, Gani F, Gargano D, Giannattasio D, Giovannini M, Infantino A, Lombardi C, Lo Schiavo M, Madonna F, Maniscalco M, Meriggi A, Milanese M, Montera C, Pio A, Russo M, Salzillo A, Scavalli P, Scichilone N, Sposato B, Stanzola A, Starace A, Vatrella A, D'Amato G, Passalacqua G. Non-respiratory symptoms in asthma as possible predictors of exacerbations. *J Allergy Clin Immunol Pract* 2015; 3:798-800.
- Ritz T, Kullowatz A, Goldman MD, Smith HJ, Kanniss F, Dahme B, Magnussen H. Airway response to emotional stimuli in asthma: the role of the cholinergic pathway. *J Appl Physiol* 2010; 108:1542-1549.
- Liccardi G, Salzillo A, Calzetta L, Cazzola M, Matera MG, Rogliani P. Can bronchial asthma with a highly prevalent airway (and systemic) vagal tone be considered an independent asthma phenotype? Possible role of anticholinergics. *Respir Med* 2016; 117:150-153.
- Liccardi G, Salzillo A, Calzetta L, Ora J, Cazzola M, Matera MG, Rogliani P. Can an increased cholinergic tone constitute a predictor of positive response to tiotropium in patients with moderate asthma? *J Allergy Clin Immunol Pract* 2016; 4:791-793.
- Liccardi G, Calzetta L, Salzillo A, Piccolo A, Pane G, Rogliani P. Can a better patient phenotyping predict the efficacy of tiotropium in asthmatic adolescents? *Expert Opin Pharmacother* 2017; 18:833-835.
- Zannin E, Pellegrino R, Di Toro A, Antonelli A, Dellacà RL, Bernardi L. Parasympathetic stimuli on bronchial and cardiovascular systems in humans. *PLoS One* 2015; 10:e0127697.
- Peters SP, Bleecker ER, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, Boushey HA, Calhoun WJ, Castro M, Cherniack RM, Craig T, Denlinger LC, Engle LL, Dimango EA, Israel E, Kraft M, Lazarus SC, Lemanske RF Jr, Lugogo N, Martin RJ, Meyers DA, Ramsdell J, Sorkness CA, Sutherland ER, Wasserman SI, Walter MJ, Wechsler ME, Chinchilli VM, Szeffler SJ. Predictors of response to tiotropium versus salmeterol in asthmatic adults. *J Allergy Clin Immunol* 2013; 132:1068-1074.
- Oland AA, Booster GD, Bender BG. Integrated behavioral health care for management of stress in allergic diseases. *Ann Allergy Asthma Immunol* 2018; 121:31-36.