Asthma control and psychological health in pediatric severe asthma: Why is child phenotyping necessary? Suggestions from a multidisciplinary "Stress-Asthma Working Group".

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Short title: Increased cholinergic tone as possible link between anxiety and asthma severity in children.

Key words: anxiety, anticholinergics, asthma phenotype, bronchial asthma, increased cholinergic tone, long-acting muscarinic antagonists, pediatric severe asthma, stress, tiotropium

Summary statement: An increased basal cholinergic tone, induced by psychological health impairment, could be a likely link between psychological/psychiatric disorders and severe bronchial asthma in children, as well as in adolescents and adults. This link can explain the high rate of anxiety in asthmatics in comparison to non-asthmatics of all ages.

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To the Editor

We read with interest the excellent article of Griffiths D et al [1]. dealing with the important association between psychological health impairment and asthma control in pediatric severe asthma. The Authors have shown a high rate of psychological disorders in pediatric patients with severe asthma. They found also that increased symptoms of anxiety or depression, assessed with a simple 4−question clinical survey, was highly associated with poor asthma control, but not with decreased lung function, in female children. We agree with the conclusions regarding the clinical aspects of mental health impairment and severe asthma in children. Similar findings have been observed also in adolescents and adults with asthma.

Anxiety and asthma are two common clinical conditions and, consequently, the risk of overlap is high, but it cannot be the only reasonable explanation of this relationship.

Since this is a pulmonology journal, we are interested to underline possible mechanisms to interpret this so frequent reported co-existence of stress/anxiety and severe asthma in children.

The Authors have not elaborated deeply on the causal and temporal association between psychological health impairment and asthma outcomes. In fact, it is not so straightforward that poor asthma control is the cause of patient's psychological status and not the other way around, because the causation may also be in the opposite direction. Actually, both directions are reasonable.

In our opinion further explanations are possible, but they have not been considered in the article.

We have previously shown that about 63% of asthmatics report the regular occurrence of at least one non-respiratory symptom (n-RS) before an asthma attack [2]. N-RSs were significantly more frequent in persistent moderate/severe asthma, than in intermittent/persistent mild asthma. About half of the patients (44%) reported n-RSs within 3 hours of the onset of an asthma attack, and similar results have been observed also in children. Behavioural symptoms such as anxiety and, to a lesser extent, depression, represented the most common n-RSs in our study [2]. This finding confirms the possible role of anxiety disorders in the development and triggering of an asthma attack. Studies have shown that psychological stress may enhance bronchial hyperreactivity through several mechanisms, such as mast cell activation and mediator release, inflammation and imbalance of the autonomic system. Both in vitro and clinical studies established a significant relationship between psycho-social stress and stimulation of the cholinergic system. Ritz and colleagues examined the respiratory responses of asthmatics after a psychological stress induced by vision of bloody films or other visual stimulations [3]. The authors concluded that an increased vagal tone could be responsible for the increased airway resistance, via a faster vagal-mediated onset response (after 1-2 minutes following the stimulus) [3].

It is likely that some symptoms induced by cholinergic hyperactivity/hyperactivation, such as those determined by psychological stress, could be present together with parasympathetic-associated RSs, as

those elicited by airway narrowing themselves. On the basis of these considerations, we suggest that attention should be focused on considering the role of the parasympathetic system as a trigger of bronchial obstruction in asthmatic children (as well as in adolescents and adults) reporting cholinergic-related n-RSs (particularly stress/anxiety) before an asthma attack. Indirectly, the results of our study [2] confirmed the assumption that cholinergic pathway is a determinant component of broncho-constriction, at least in a subset of asthmatic patients. We have hypothesized that, in some individuals, a high basal cholinergic tone might play a more predominant role in determining airway obstruction, compared with other well-known factors such as allergens/air pollutants, infections, exercise etc. (a distinct and definite "asthma phenotype"?).[4]

The anxiety/stress-induced vagal hyperactivity in asthmatics offers the opportunity to discuss some aspects from a therapeutic point of view. In fact, we could postulate that blocking muscarinic pathway at the airway smooth muscle level might be more beneficial to control airway obstruction and mucus secretions in asthmatics with high basal parasympathetic tone.

Although the tolerability and efficacy of anticholinergic agents (especially long-acting muscarinic antagonists [LAMAs]) have been investigated in asthmatic children/adolescents/adults, we believe that LAMAs should be further considered in patients with increased basal cholinergic activity.

The 2020 NAEPPCC update[5] recommends the use of LAMA (tiotropium) as alternative and preferred treatment in step 3/4 and step 5, respectively, in addition to inhaled corticosteroids + long acting $ß_2$ agonists (ICS-LABA) in children aged 12 years and older with persistent asthma. In these patients with uncontrolled persistent asthma, LAMA add-on offers a small benefit. However, no LAMA is recommended in children with persistent asthma aged 5-11 by the Expert Panel. They did not examine the role of LAMA treatment in this population, because the key questions and systematic reviews did not address this age group.

The Expert Panel indicates also future research opportunities for LAMAs, e.g. their clinical impact in real-world settings, systematic reviews on their use in children with asthma aged 6 to 11 years, role of LAMAs other than tiotropium as add-on therapy. In addition, LAMAs are already recommended in children 6-11 years old, by GINA (GINA report, 2020 update).

Considering this background, we suggest a new future research opportunity such as the necessity of an adequate phenotyping also of asthmatic children who could benefit from the use of LAMAs through the evaluation of basal cholinergic tone. Methacholine inhalation, slow deep breathing, assessment of the respiratory system resistance by multiple frequency forced oscillation technique (FOT), measurement of resting heart rate, respiratory sinus arrhythmia (RSA), and pupillometry constitute the most efficacious methods for evaluation of the degree of vagal tone in children. These assessments may help to find possible LAMA high-responders (Figure 1). Finally, this characterization of LAMA responders may be particularly useful when LABAs are not recommended for efficacy or safety reasons (i.e. due to poor efficacy or adverse events) and for steroid-sparing purposes.

In conclusion, the relationship between anxiety and asthma is a complex puzzle which needs further studies for a better understanding of the underlying mechanisms. The currently available literature has shown that anxiety and related psychological disorders are likely to be involved as relevant factors, together with other well-established individual/environmental risk factors, in the pathological mechanisms leading to airway inflammation, the onset of clinical symptoms, as well as exacerbations of respiratory symptoms in asthma. Therefore, anxiety can be responsible for scarce or non-adherence to their medical regimens, poor symptom control and poor treatment outcomes leading to impaired health-related quality of life, both in adults and in children with asthma, through several mechanisms.

Adequate educational programs should be planned for all asthmatic patients suffering from psychological disorders. This approach requires particular attention in children in order to obtain a better control of respiratory symptoms and prevent asthma progression and remodeling.

Declaration of Interest

M. Martini is an employee of Chiesi Farmaceutici S.p.A. All the other authors declare that they have no conflict of interest. The study has been carried out without any financial support.

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Figure 1.

Decision tree – assessment and treatment of cholinergic “asthma phenotype” in children with severe asthma.