

From THE DEPARTMENT OF WOMEN'S AND
CHILDREN'S HEALTH
Karolinska Institutet, Stockholm, Sweden

**INVESTIGATING
PROBLEMATIC SEVERE ASTHMA
IN CHILDREN
– A TRANSLATIONAL APPROACH**

Jon R Konradsen



**Karolinska
Institutet**

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Abstract

Children with problematic severe asthma (PA) have persistent symptoms and/or severe exacerbations despite treatment with high doses of currently available asthma medications. The term PA includes children who are difficult to treat due to unidentified exacerbating factors (e.g. allergens or environmental hazards, comorbidities, psychological and social issues, and/or poor adherence) and those lacking identifiable aggravating factors but, nonetheless, do not respond well to asthma therapy. Children with PA are a heterogeneous group of patients with varying clinical presentations, pulmonary function and patterns of inflammation.

This thesis is based on the results of a Swedish nationwide cross-sectional study in which school aged children with PA (n=57) were compared to age matched peers with persistent, but controlled asthma (CA), (n=39). The major objectives were to identify distinguishing features of children suffering from PA, to differentiate between children who were difficult to treat and those who were severely resistant to therapy and to investigate novel and potentially clinical relevant biomarkers of PA. PA was defined by insufficient asthma control despite high doses of inhaled corticosteroids.

The protocol included a detailed characterization of: history and clinical presentation; pulmonary function; bronchial hyperresponsiveness; inflammatory biomarkers in blood (including white blood cells, interleukin-5 and chitinases (chitotriosidase and the chitinase-like protein YKL-40)), urine (EPX) and exhaled air (FeNO); allergy (IgE antibodies, component resolved allergy diagnostics, basophil allergen threshold sensitivity (CD-sens)); morphology (computerized tomography of sinuses and lungs (in the PA group only)).

The major distinguishing features of children with PA involve familial background (heredity, socioeconomic status), clinical presentation (comorbidities and triggering factors) and pathophysiological differences including degree of airway obstruction, bronchial hyperresponsiveness and inflammatory profile (IL-5, number of eosinophilic and neutrophilic cells in blood). Sixty percent of children with PA had therapy-resistant asthma, with the remainder being difficult to treat due to identified aggravating factors.

Individual IgE-responses were similar between children with PA and CA. Children with PA were more often multi-sensitized to > 3 single lipocalin (nMus m 1, rEqu c 1, Fel d 4, rCan f 1, 2), kallikrein (rCan f 5) and secretoglobulin (rFel d 1) allergens compared to children with CA. Cat-allergic children with PA had higher allergen sensitivity, as measured by CD-sens, compared to cat-allergic peers with CA. Furthermore, CD-sens correlated with clinical markers of asthmatic disease, including asthma control and biomarkers of eosinophilic inflammation.

YKL-40 levels and chitotriosidase activity were increased in the serum of children with PA, and YKL-40 specifically correlated with airway remodelling (as assessed by computerized tomography) and blood neutrophils in children severely resistant to asthma therapy.

By employing a comprehensive and standardized clinical assessment we have discerned specific features of children with PA and identified children who are severely resistant to therapy. We have applied two novel methods of allergy diagnostics (Component resolved diagnostics and CD-sens) and found that these two methods provide relevant information when investigating children with PA. Finally, our findings confirm that YKL-40 is a potential biomarker of asthma severity and airway remodeling. A translational research approach is necessary when investigating associations between disease mechanisms and clinical presentation in complex diseases.

LIST OF PUBLICATIONS

The thesis is based on the following papers. The papers will be referred to by their Roman numerals (I-IV).

- I. **Konradsen JR**, Nordlund B, Lidegran M, Pedroletti C, Grönlund H, van Hage M, Dahlen B, Hedlin G; In Cooperation with the Swedish network of Pediatric Allergists, Severe Asthma Network.
Problematic severe asthma: A proposed approach to identifying children who are severely resistant to therapy.
Pediatr Allergy Immunol. 2011 Feb;22(1 Pt 1):9-18. doi: 10.1111/j.1399-3038.2010.01098.x. Epub 2010 Sep 30. PMID: 20880352.
- II. Nordlund B, **Konradsen JR**, Kull I, Borres M, Önell A, Hedlin G, Grönlund H.
IgE antibodies to animal-derived lipocalin, kallikrein and secretoglobulin are markers of bronchial inflammation in severe childhood asthma.
Allergy. 2012 Feb 17. doi: 10.1111/j.1398-9995.2012.02797.x
PMID: 22339365 [Epub ahead of print].
- III. **Konradsen JR**, Nordlund B, Nilsson Ola B, van Hage M, Nopp A, Hedlin G, Grönlund H.
High basophil allergen sensitivity is associated with severe allergic asthma in children.
Pediatr Allergy Immunol. 2012 Mar 21. doi: 10.1111/j.1399-3038.2011.01260.x.
PMID: 22432913 [Epub ahead of print].
- IV. **Konradsen JR***, James A*, Nordlund B, Reinius L, Melén E, Söderhäll C, Wheelock Å, Lödrup Carlsen K, Lidegran M, Verhoek M, Boot R, Dahlén B, Dahlén SE, Hedlin G.
* Have contributed equally to the preparation of this manuscript.
Chitinases are markers of airway remodeling in children with therapy resistant asthma.
Submitted.