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BRIEF REPORT

YKL-40 is a proposed biomarker of inflammation and remodelling elevated in children with bronchopulmonary dysplasia compared to asthma

YKL-40 is a chitinase-like, secreted glycoprotein associated with several respiratory disorders, including asthma and oxidant-induced lung injuries.[1] Its biological role remains unclear, but it correlates with markers of airway fibrosis and remodelling in asthma, where it has emerged as a candidate biomarker for non-type 2 inflammation.[2]

Bronchopulmonary dysplasia (BPD) is a chronic disorder, characterised by underdeveloped, damaged lungs following premature birth and mechanical ventilation, whereas asthma is a chronic inflammatory disease, often associated with atopy and reversibility in children.[3] BPD has been associated with more airway fibrosis and non-reversible lung function impairment than asthma. Although airway obstruction is generally fixed in BPD, and variable in asthma, bronchial hyper-responsiveness may be present in both.[3] Children with both diseases may experience wheeze and obstruction and receive similar treatment.

This cross-sectional study investigated YKL-40 as a potential biomarker of airway inflammation and remodelling in a previously described cohort[3] of 10-year-old children: 27 with mild allergic asthma and sensitisation to inhaled allergens, and 28 with BPD.

YKL-40 levels were assessed against clinical characteristics, including lung function, bronchial hyper-responsiveness, continuous positive airway pressure (CPAP) therapy, exhaled nitric oxide and circulating inflammatory cytokines interleukin (IL)-1β, IL-8 and tumour necrosis factor alpha (TNFα).

BPD was defined by supplementary oxygen requirement at 28 days, with severity determined at 36 weeks of gestation. The asthma group had no neonatal history of respiratory symptoms, assisted ventilation or respiratory treatment. Data were collected regarding atopic status, bronchial hyper-responsiveness, exhaled nitric oxide, lung function using both spirometry and plethysmography, and respiratory health by questionnaires. Serum YKL-40 was analysed by enzyme-linked immunosorbent assay (R&D Systems) and cytokines (IL-1β, IL-8 and TNFα) at the routine hospital laboratory. Parents and children provided written, informed assent and consent and the Karolinska Institutet ethics committee approved the study.

The BPD group had reduced pulmonary function measurements, including forced expiratory volume in one second (FEV_1) and FEV_1/forced vital capacity (FVC) ratio, lower carbon monoxide diffusion capacity, lower exhaled nitric oxide and used less asthma medication.[3] Serum YKL-40 was significantly higher in BPD than asthma (Figure 1A), and when CPAP for BPD exceeded one month (Figure 1B).

Spearman rank correlations between serum YKL-40 and clinical characteristics were examined and showed that higher YKL-40 was associated with lower lung function in BPD (FEV_1% predicted rho = −0.41, $P = 0.03$; FVC % predicted rho = −0.41, $P = 0.03$) and higher concentrations of IL-8 (rho = 0.43, $P = 0.02$) and TNFα (rho = 0.49, $P = 0.01$). In asthma, no significant relationships were observed between YKL-40 and any other variables.

Taken together, we found higher YKL-40 in 10-year-old children with BPD compared to asthma. There were also associations between higher YKL-40 levels and lower pulmonary function in BPD, as well as duration of CPAP therapy. We believe this is the first examination of YKL-40 in children with BPD at school age, when the disease has progressed beyond the acute stage, and it is intriguing that a difference compared to asthma is observed.

Elevated YKL-40 in BPD may reflect the high degree of lung fibrosis and structural alterations associated with this disorder.[3,4] YKL-40 is involved in many processes relevant to fibrosis, including smooth muscle and fibroblast proliferation.[1] Accordingly, YKL-40 correlates with indices of airway remodelling, including bronchial wall thickness and subepithelial fibrosis.[1,5] In BPD children, YKL-40 reflected disease severity, where higher levels related to lower FEV_1 and FVC, and longer CPAP. The latter could involve greater oxidative stress, more barotrauma due to respiratory therapy or a greater need for CPAP due to more severe lung disease caused by prematurity.

Higher YKL-40 in BPD could also relate to neutrophilic inflammation, although the biological mechanisms require further investigation. Children with chronic BPD and persistent airway obstruction have demonstrated ongoing neutrophilic inflammation, with increased sputum neutrophils and IL-8.[4] Here, YKL-40 correlated with IL-8 and TNFα, cytokines involved in neutrophil function, thus supporting the proposed involvement of YKL-40 in non-type 2 and neutrophilic inflammation.[2,5]

No significant relationships were observed between YKL-40 and airway inflammation or lung function in asthma, probably because

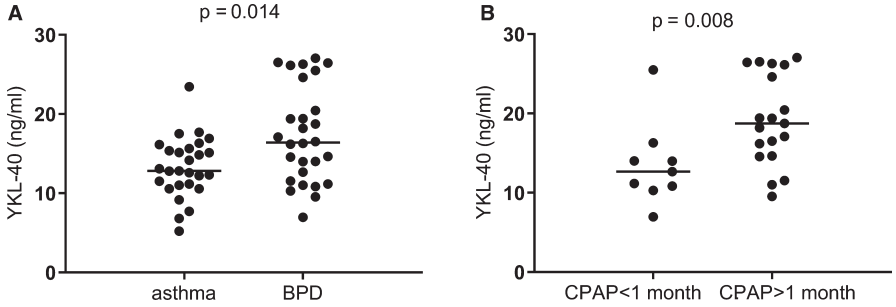

FIGURE 1 A, Serum YKL-40 levels in children with asthma and BPD. B, Serum YKL-40 levels in children with BPD treated with CPAP for less than or greater than 1 mo. Results are shown as individual data points with a median bar. Comparisons were performed using Mann-Whitney non-parametric tests

our cases were relatively mild and atopic. Previous studies have described the involvement of YKL-40 in more severe, non-type 2, neutrophilic asthma phenotypes in children and adults.[2,5] The asthma cases in this study had similar, but not directly comparable, YKL-40 levels to the healthy schoolchildren in our previous study.[5]

Our finding of higher YKL-40 in children with BPD than asthma, together with the associations between YKL-40 and disease severity, provides new information regarding its role as a biomarker of respiratory disease. YKL-40 could be useful in distinguishing asthma from BPD and could also indicate the degree of airway dysfunction in BPD.

KEYWORDS

asthma, biomarker, bronchopulmonary dysplasia, YKL-40

CONFLICT OF INTEREST

None.

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Anna J. James[1]
Björn Nordlund[2,3]
Jon R. Konradsen[2,3]
Christina Ebersjö[4,5]
Sven-Erik Dahlén[1]
Eva Berggren Broström[4,5]
Gunilla Hedlin[2,3]

[1]*Experimental Asthma and Allergy Research, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden*

[2]*Astrid Lindgren Children's Hospital, Lung and Allergy Unit, Karolinska University Hospital, Stockholm, Sweden*

[3]*Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden*

[4]*Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden*

[5]*Sach's Children and Youth Hospital, Södersjukhuset, Stockholm, Sweden*

Correspondence

Anna J. James, Experimental Asthma and Allergy Research, Institute of Environmental Medicine, Karolinska Institutet, Biomedicum 5B, Solnavägen 9, 171 77 Stockholm, Sweden.
Email: anna.james@ki.se

ORCID

Anna J. James https://orcid.org/0000-0003-2698-8419
Björn Nordlund https://orcid.org/0000-0001-9888-1659
Jon R. Konradsen https://orcid.org/0000-0001-7745-8624
Christina Ebersjö https://orcid.org/0000-0002-7578-8555
Sven-Erik Dahlén https://orcid.org/0000-0002-4993-4002
Eva Berggren Broström https://orcid.org/0000-0001-8441-5497
Gunilla Hedlin https://orcid.org/0000-0001-7737-6506

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