Asthma and co-morbid conditions: nasal polyps

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### Prevalence of nasal polyps and association with asthma

<table>
<thead>
<tr>
<th>Population</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td><strong>General population</strong></td>
<td></td>
</tr>
<tr>
<td>by history</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td><strong>Asthma population</strong></td>
<td></td>
</tr>
<tr>
<td>general</td>
<td>7% - 15%</td>
</tr>
<tr>
<td>non atopic</td>
<td>13%</td>
</tr>
<tr>
<td>atopic</td>
<td>5%</td>
</tr>
<tr>
<td><strong>AERD</strong></td>
<td></td>
</tr>
<tr>
<td>nasal polyps</td>
<td>36% - 96%</td>
</tr>
</tbody>
</table>
Association of CRS with asthma

- CRS coexisted in 34% patients with asthma (Annesi–Maesano 1999)
- Abnormal sinus radiographs can be found in 53% of asthmatics (Berman S 1974)
- Mucosal thickening (CT scans) can be visualized in 74% of patients with asthma (Pfister R 1994)
- Asthmatics with CRS are more likely to have NPs, than non asthmatics with CRS (57.6% versus 25%) (Pearlman AN 2009)
Asthma and NP – GA2LEN Survey

• The Global Allergy and Asthma Network of Excellence (GA2LEN) conducted a postal questionnaire in representative samples of adults living in Europe to assess the presence of asthma and CRS defined by the EP3OS criteria.

• **Results:** Over 52 000 adults aged 18-75 years and living in 19 centers in 12 countries took part.

• In all centers, there was a strong association of asthma with CRS (adjusted **OR: 3.47; 95% CI: 3.20-3.76**) at all ages.

• The association with asthma was stronger in those reporting both CRS and allergic rhinitis (adjusted **OR: 11.85; 95% CI: 10.57-13.17**).

Jarvis D et al. Allergy 2011,
Chronic rhinosinusitis with and without nasal polyps

<table>
<thead>
<tr>
<th>Sign and Symptoms</th>
<th>CRS with NP</th>
<th>CRS without NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Nasal obstruction</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Loss if smell</td>
<td>Postnasal drip</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Eosinophylia ECP</td>
<td>MNC,PMN MPO</td>
</tr>
<tr>
<td>T cell polarization</td>
<td>TH2 type IL-5</td>
<td>TH1 type IFN γ</td>
</tr>
<tr>
<td>T-regulatory cells/factors</td>
<td>FOXP3 decreased TGF β 1 lower</td>
<td>FOXP3 normal TGFβ1 normal</td>
</tr>
<tr>
<td>Remodeling</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Association with asthma</td>
<td>Strong</td>
<td>Weak</td>
</tr>
</tbody>
</table>

Asthma and eosinophylic inflammation in NP.

- Asthma is more prevalent in white European (mostly eosinophylic polyps) as compared to Asian patients with mostly neutrophyllic CRS/NP.
- Eosinophylic inflammation (with IL5 protein production) is associated with asthma in both populations.
- Other factors (sIgE to SAE in NP) seem to be associated with asthma.

VanBruaene et al. 2008
Bachert et al. 2010
CRS/NP and asthma severity

- CRS is associated with more severe asthma (Liou A et al. Chest 2003)

- Presence of CRS (but not rhinitis) is associated with multisymptom (more severe asthma) (Lotvall J et al. Resp res 2010)

- CRS related to more severe asthma: higher medication use and lower FEV1 (Aazami et al. Iran JACI 2009)
A group of 136 (63) patients with difficult to control asthma divided into 2 groups
- One exacerbation per year
- Three or more per year

- All patients had at least one of the above factors
- 52% showed three or more factors

OR=3.6

Ten Brinke et al. 2005
Mechanisms linking CRS/NPs with asthma

- Neurogenic reflex
- Mouth breathing
- Aspiration
- One airway disease – involvement of bone marrow
- Common triggers
  - Infectious factors
  - Allergens
  - Other environmental (e.g. tobacco smoke)
CD34/CD45+ cells and CFC are present in nasal polyps

- Immunoreactive CD34+/CD45+ mononuclear cells are present within nasal polyps
- Isolated polyp mononuclear cells demonstrated myeloid colony formation with presence of CD34+/CD45+ cells (assessed by flow cytometry)

Kim YK et al. AJRCMB 1999, 20, 388
Eosinophil progenitors in peripheral blood and asthma severity.

Eosinophil progenitors (CD 125+/CD34+/CD45+)

Correlation of (CD 125+/CD34+/CD45+) cells with FEV1

Systemic reaction to aspirin bronchial challenge – recruitment of eosinophil progenitors

19 AERD patients were challenged with lysin aspirin and CD34+ cells in PB were determined. In half of patients positive bronchial reactions were associated with extra bronchial symptoms:

CD34+/CD45+/CD125+ cells

Eotaxin-2

Mechanisms linking CRS/NP. with asthma

- Neurogenic reflex
- Mouth breathing
- Aspiration
- One airway disease – involvement of bone marrow
- Common triggers
  - Infectious agents
  - Allergens
  - Other environmental (e.g. tobacco smoke)
# Role of Infectious factors in CRS/NPs and asthma exacerbations

<table>
<thead>
<tr>
<th></th>
<th>CRS/NP</th>
<th>Asthma</th>
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<tbody>
<tr>
<td>Viruses</td>
<td>Unknown</td>
<td>Important</td>
</tr>
<tr>
<td>Fungi</td>
<td>Controversial (EFRS)</td>
<td>Not likely</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Superinfections</td>
<td>Controversial – mostly atypical bacteria</td>
</tr>
<tr>
<td>Staphylococal colonization</td>
<td>66-87%</td>
<td>No</td>
</tr>
<tr>
<td>Bacterial superantigens</td>
<td>?</td>
<td>?</td>
</tr>
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**SAE-IgE and eosinophylic inflammation**

- Specific IgE to SAE are present in nasal polyps tissue.
- sIgE to SAE are related to eosinophylic inflammation in rhinosinusitis.
- Eosinophylic inflammation in NPs (with IL5 protein production) is associated with asthma.
- SAE-IgE in NP is associated with asthma.
  - OR = 5.8 (95% CI 1.8-29.6%)

**Conclusions:**

- SAE-IgE may amplify the eosinophylic inflammation and IgE formation increasing the risk of asthma comorbidity.

- VanBruaene et al. 2008
- Bachert et al. Al. 2010
Characteristics of patients with severe and non-severe asthma (i)

- Patients were recruited from one asthma clinic (Allergy and Asthma Centre in Lodz)
- Severe asthma defined according to the ATS Workshop 2000
- Non-severe asthma – mild and moderate
- Patients were followed up for at least 12 months

<table>
<thead>
<tr>
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<th>Severe (=109)</th>
<th>NS (n=105)</th>
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<tbody>
<tr>
<td>Exacerbations/year</td>
<td>1.96±1.48</td>
<td>0.37±0.61*</td>
</tr>
<tr>
<td>FEV1/FVC%</td>
<td>63.0±12.5</td>
<td>78.8±9*</td>
</tr>
<tr>
<td>MEF25-75(l/s)</td>
<td>43.2 ± 23</td>
<td>85.3 ±28*</td>
</tr>
<tr>
<td>Inhaled GCS (µg/day)</td>
<td>1660 ± 0.550</td>
<td>590 ± 200*</td>
</tr>
<tr>
<td>Oral GCS (mg/day)</td>
<td>7.8</td>
<td>0</td>
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</tbody>
</table>

M.L. Kowalski et al. Allergy 2011, 66,32-38
sIgE to Staphylococcus aureus enterotoxins in serum and asthma severity

sIgE to SAE in severe and non-severe asthmatics

Serum ECP in SAE (+) and SAE (-) asthmatics

Serum concentrations of sIgE to SAE was similar in ASA-tolerant and ASA-sensitive asthmatics

M.L. Kowalski et al. Allergy 2011, 66,32-38
Effect of medical treatment of CRS on bronchial asthma

- Improvement in asthma in 4 patients treated for CRS (Slavin RG 1982)
- 79% of children stopped using bronchodilators following CRS treatment with antibiotics (Rachalevsky GS 1984)
- Spirometry normalized in 67 children with asthma treated for CRS (Friedman R 1994)
- Improvement in severity of asthma and PF in 18 children treated with INS/antibiotics (Tosca 2003)
- Of 48 patients 18 responded to INCS (600ug/d for 6 wks) and had maintained pulmonary function (Lamblin C et al. 2000)
Effect of endoscopic sinus surgery (ESS) on asthma

- Significant reduction in asthma severity (65%), hospitalizations (75%) and emergency visits (81%) (Nishioka GJ 1994)
- ESS improved pulmonary function in patients with asthma (Ikeda K 1999)
- Improvement in asthma symptoms and oral steroids one year after ESS (Palmer JN 2001)
- Decrease in non-specific BHR after ESS (Okayama M 1998)
- Improvement in asthma symptoms and PEFR (Enhage A 2009)
- Improvement in symptoms, decrease in asthma medication and in hospitalizations (Proimos E 2010)
Effect of medical versus surgical CRS/NP therapy on asthma

Patients
- 43 patients with and without NPs and concomitant asthma were randomized to either medical (erythromycin, nasal douches, INCS) or surgical treatment (ESS followed by erythromycin, nasal douches) and were assessed at 6 and 12 months.

Results
- Both medical and surgical treatment were associated with subjective and objective improvement in asthma.
- Improvement in CRS symptoms correlated with improvement in asthma symptoms and control.

Ragab S et al. ERJ 2006, 28, 68
Aspirin desensitization in patients with AERD

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1923</td>
<td>F. Vidal reported „desensitization” to aspirin</td>
</tr>
<tr>
<td>1976</td>
<td>C. R. Zeiss &amp; R.F. Lockey described refractory period to aspirin</td>
</tr>
<tr>
<td>1981</td>
<td>D.D. Stevenson reported clinical benefits of prolonged treatment with aspirin after desensitization</td>
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</tbody>
</table>
Clinical efficacy of ASA-desensitization in AERD

- 11 studies assessed clinical efficacy of ASA after desensitization
- Total 474 patients were successfully desensitized
- Only 1 study was placebo controlled (Stevenson 1984)
- Duration of treatment: 2 weeks - 6 years
- Dosing of aspirin: 325 mg-2600 mg
- Clinical assessment: symptoms; need for medicines; exacerbations, polyps recurrence
- Full data available for limited number of patients

% of patients with clinical improvement while on aspirin

- Asthma: 42% improvement, 58% no improvement
- CRS: 36% improvement, 64% no improvement
- Asthma/CRS: 13% improvement, 87% no improvement
Conclusions

- CRS with NP is associated with bronchial asthma and may affect asthma severity
- The pathomechanisms of CRS/NP and asthma association is complex
- Proper management of CRS/NP may improve asthma symptoms
- New treatment modalities common for both diseases are needed
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