Non-Allergic Rhinitis and Asthma

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Royal National Throat Nose & Ear Hospital
London
Disclosures

Research funds:
ALK-Abello, GSK ,

Advisory Boards:
ALK-Abello, Allergen Therapeutics, GSK, Merck, Uriach, USB

Speaker/Chair:
ALK-Abello, GSK , Merck, Uriach
Learning Objectives

- Classification & phenotypes NAR

- Co-morbid asthma association- or lack of it

- (Diagnosis and treatment of NAR-see www.bsaci.org)
Rhinitis – allergic and non-allergic precedes asthma

Cumulative incidence rate of asthma

Shaaban R. Et al., The Lancet, 2008
Non-allergic global AW disease

NON-ALLERGIC RHINITIS

ASTHMA

PROBLEMS

heterogeneity of non-allergic rhinitis

rhinitis - rhinosinusitis
Heterogeneity of non-allergic rhinitis

Allergic rhinitis
undiagnosed
local IgE production

Occupational-
Allergic & non-
allergic

Infectious

Medication induced

Non-allergic rhinitis

Hormonal

Rhinosinusitis
w/wo
nasal polyps

Idiopathic
Inflammatory & Non-inflammatory
Heterogeneity of non-allergic rhinitis

Non-allergic rhinitis
- undiagnosed
- local IgE production

Non-allergic rhinitis
- occupational
- non-allergic

Infectious

Hormonal

Non-allergic rhinitis
- with/without nasal polyps

Medication induced

Idiopathic
- Non-inflammatory
Potential mechanisms of Idiopathic Rhinitis

**Stimuli**

- Sensory Nerve Activation & Hyperresponsiveness
  - Local IgE response
  - Inflammatory Mediator Release
  - Mast cell activation (non-IgE mediated)

**Inflammation**

- Epithelial Activation
- Epithelial Damage
- INFLAMMATION
- Local IgE response

**Sensory Nerve Activation & Hyperresponsiveness**

- Local release of neuropeptides
- Recruitment of parasympathetic reflexes, sneeze, itch

**Vascular Symptoms**

- Vascular Congestion
- Vascular Leakage
- Mucus Secretion
- Sneezing & Itch

**Glandular & Vascular hyperresponsiveness**

- Sympathetic & Parasympathetic imbalance
Heterogeneity of non-allergic rhinitis

- **ALLERGIC RHINITIS**
  - undiagnosed
  - local IgE production

- **OCCUPATIONAL**

- **INFECTIONOUS**

- **HORMONAL**

- **NON-ALLERGIC RHINITIS**
  - w/wo nasal polyps

- **RHINOSINUSITIS**
  - w/wo nasal polyps

- **MEDICATION induced**

- **IDIOPATHIC**
Physiologic circumstances

Protection

air filtering
air conditioning
air humidification
Physiologic circumstances

Protection
air filtering
air conditioning
air humidification

Nasal disease
Trigger
TRIGGER SYNERGY IN ASTHMA

- **Allergen**
  Increased BHR-most allergens stay in nose.

- **Infection** - viral rhinitis causes BHR
  Rhinovirus present in nose in asthma exacerbations.

- **Both - synergy**

Sensitisation, Exposure and the Risk Hospital Admission Children

Murray, Custovic et al 2005
Heterogeneity of non-allergic rhinitis

ALLERGIC rhinitis
undiagnosed
local IgE production

OCCUPATIONAL

INFECTIOUS

HORMONAL

NON-ALLERGIC RHINITIS
w/wo nasal polyps

RHINOSINUSITIS

MEDICATION induced

IDIOPATHIC inflammatory
Global Airway Disease

NON-ALLERGIC RHINITIS WITH EOSINOPHILS

ASTHMA

FACTS

- similar pathophysiology
- mucosal IgE
- risk factor
- ?progression to AERD
## Sinonasal disease in asthma & COPD

<table>
<thead>
<tr>
<th></th>
<th>ASTHMA</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>Age</td>
<td>42.74 ± 2.99</td>
<td>65.65 ± 1.68</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (41%)</td>
<td>27 (87%)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (59%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>2 (6%)</td>
<td>9 (29%)</td>
</tr>
</tbody>
</table>

Hens G and Hellings P, Allergy, 2008
## Sino-nasal VAS scores

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<tr>
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<th>ASTHMA</th>
<th>COPD</th>
</tr>
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<tbody>
<tr>
<td><strong>Mean ± SEM</strong></td>
<td><strong>Allergic patients</strong></td>
<td><strong>Non-allergic patients</strong></td>
</tr>
<tr>
<td>P&lt;0.05</td>
<td>3.77 ± 0.56</td>
<td>3.47 ± 0.56</td>
</tr>
<tr>
<td>P&lt;0.01</td>
<td>2.23 ± 0.36</td>
<td>2.54 ± 0.60</td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td>2.32 ± 0.46</td>
<td>2.35 ± 0.66</td>
</tr>
<tr>
<td></td>
<td>2.83 ± 0.43</td>
<td>3.26 ± 0.54</td>
</tr>
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<td></td>
<td>3.65 ± 0.58</td>
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Hens G and Hellings P, Allergy, 2008
# Nasal lavage fluid analysis

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<tr>
<td><strong>Th2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-5</td>
<td>Below detection limit in nearly all samples</td>
<td></td>
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<td><strong>Th1</strong></td>
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<td></td>
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<tr>
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<td></td>
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<td></td>
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<tr>
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Heterogeneity of non-allergic rhinitis

- Allergic rhinitis
  - undiagnosed
  - local IgE production
- Occupational
- Infectious
- Hormonal
- Non-allergic rhinitis
- Rhinosinusitis
  - w/wo nasal polyps
- Medication-induced
- Idiopathic
Heterogeneity of non-allergic rhinitis

- ALLERGIC rhinitis
  - undiagnosed local IgE production
- OCCUPATIONAL-Allergic & non-allergic
- INFECTIOUS
- HORMONAL
- NON-ALLERGIC RHINITIS
  - RHINOSINUSITIS w/wo nasal polyps
- MEDICATION induced
- IDIOPATHIC Inflammatory & Non-inflammatory
Further investigation of rhinitis

- **History + ve**
  - SPTs − ve

Further SPTs suggested by history (e.g. latex, pet, occupational allergen)

- + ve
  - **ALLERGIC RHINITIS**
  - + ve

Nasal allergen challenge(s) (according to history) or nasal aspirin challenge

- + ve
  - **Non-allergic Rhinitis with Eosinophilia Syndrome (NARES)**

Check for inflammation
- − ve
  - nasal smear for eosinophils (↑nNO may be a substitute)

- + ve
  - **Non-allergic Non-inflammatory Rhinitis (NINAR)**

? neurogenic

- − ve
  - Oral aspirin challenge

- − ve
  - − ve
  - + ve

ASPIRIN / NSAID SENSITIVITY

- + ve
  - − ve
“Samter’s” Triad

Asthma
Nasal polyps
Aspirin hypersensitivity

First described by Widal (1922)
WHY IS THE UPPER AIRWAY IMPORTANT?

1. AETIOLOGY & PATHOGENESIS
Site of disease onset
Availability for investigation

2. CLINICAL RELEVANCE
Need for treatment
Diagnosis-safest test for aspirin sensitivity
Specific treatment—"desensitization"
Persistent rhinitis, onset 29.7+- 12.5 years then asthma, aspirin intolerance, nasal polyposis

Earlier and more severe in females

Atopics (1 in 3 ) earlier rhinitis and asthma

? Viral induction of disease


AIANE network-data from 500 patients from 16 centres in 10 European countries

Sequential pattern emerged:

- Persistent rhinitis, onset 29.7+- 12.5 years then asthma, aspirin intolerance, nasal polyposis
- Earlier and more severe in females
- Atopics (1 in 3 ) earlier rhinitis and asthma
- ? Viral induction of disease
Normal population 0.6-2.5%

Perennial Rhinitis 6%

Asthma-21% adult onset

CRS & Nasal polyps 30-40%

Varga et al, 1994
Nasal polyps and eosinophils: often a systemic inflammation

- Increased IL-5
- Increased ECP
- Increased migration
- Increased survival
- Increased activation
- Increased maturation
- Increased differentiation
- Increased recruitment

Asthma

Chemotaxis
IL5 + Eotaxin

↑ IL-5
↓ ECP
**S. aureus** colonization and IgE antibodies to **S. aureus** enterotoxin mix in mucosal tissue

- **Controls** (n=9): Colonization 33%
- **CRS** (n=22): Colonization 27%
- **NP** (n=53): Colonization 64%
- **NP + asthma** (n=18): Colonization 67%
- **NP + ASS** (n=8): Colonization 88%

*P<0.05 vs CRS.

T. Van Zele et al.  
JACI 2004
Staph. aureus/Enterotoxin in U & L airway epithelium

T-Cell: IL-5, IL-4, IL-13

TCR, VB

Eosinophil: ECP

Plasma cell: IgE, IgA, IgG
\[ pLTs < PGE_2 \quad pLTs > PGE_2 \]

aspirin tolerant

aspirin sensitive

Yamashita et al. Rhinology 1989
Pinto et al. Prost Leuk Ess F A 1987
Gosepath et al. ORL 1999
Kowalski et al. AJRCCM 2000
Outline of eicosanoid metabolism

Membrane Phospholipids

Phospholipase

5-LO/FLAP inhibitors

5-LO

5-LO/FLAP

Arachidonic Acid

LX

LTC₄ synthase

EX

LTB₄

LTA₄

LTA₄ hydrolase

LTC₄

LTC₄ synthase

LTD₄

LTE₄

PGG₂

PGD₂

PGF₂α

PGE₂

PGI₂

Pro-inflammatory

Anti-inflammatory

CysLT₁ receptor antagonists

Aspirin/NSAI Ds COX-2 inhibitors

5-LO

COX-1

COX-2

Sun Ying et al AI 2004;53:111
Nasal lavage fluid analysis

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Rhinitis and COPD

Limited information!

Up to 88% of patients with COPD experience nasal symptoms

*Uri N et al., J Laryngol Otol, 2002*

Correlation between nasal symptoms and impairment of QOL

*Hurst J et al., Respir Med, 2004*

Involvement of upper airways in COPD

*Hens G et al., Allergy, 2008*
Relationship between IL-8 concentration in paired nasal wash fluid and sputum samples from 47 patients with COPD (r = 0.30; p = 0.039)

CRS & Bronchiectasis

Comorbidities

BRONCHIECTASIS (n=85)

- with CRS
  - 81%
- without CRS
  - 19%

- with NP
  - 26%
- without NP
  - 55%

Guilemany et al. *Allergy* 2008
CONCLUSIONS

**RHINITIS**
allergic vs non-allergic

**RHINOSINUSITIS**
with NP / without NP

**ASTHMA**

**COPD**

**EPOS**
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<th>UPPER AIRWAYS</th>
<th>LOWER AIRWAYS</th>
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<td>➔ Allergic rhinitis</td>
<td>➔ Allergic asthma</td>
</tr>
<tr>
<td>➔ NARES</td>
<td>➔ Intrinsic asthma</td>
</tr>
<tr>
<td>➔ CRS &amp; Nasal polyps</td>
<td>➔ Intrinsic Asthma</td>
</tr>
<tr>
<td>➔ AFS</td>
<td>➔ ABPA</td>
</tr>
<tr>
<td>➔ CRS</td>
<td>➔ ?panbronchiolitis/bronchiectasis</td>
</tr>
<tr>
<td>➔ Rhinitis</td>
<td>➔ COPD</td>
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• Whole airway should be considered – even by chest physicians and ENT surgeons
...who might like to work together

• URT is easily available for investigation: challenge, sampling- see soon Diagnostic tools in Rhinology an EAACI Task Force document
...and for therapy INCLUDING ASTHMA PREVENTION

• United pathways /guidelines- a start has been made.....

Children with asthma and rhinitis/ rhinosinusitis
RCPCH pathways UK 2010
ACKNOWLEDGEMENTS

Ideas and slides from

Peter Hellings Belgium

Peter Howarth, UK

Claus Bachert, Belgium

Further reading

Further marches: allergic and non-allergic
Scadding GK, CEA 2007.

Airways disease: just nosing around
Scadding GK & Kariyawasam H
Thorax 2009
NON-ALLERGIC, NON-INFECTIVE RHINITIS
TREATMENT  www.bsaci.org

Other causes eliminated
SPT-ve

Eosinophilic inflammatory

INS/Anti-LTSAnti-H1

Combination + ipratropium

Consider aspirin challenge/Rx

No inflammation-neurogenic

Ipratropium OR capsaicin