Asthma and the Unified Airway

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What we used to think

- The upper airway is separate from the lower airway.
- Different mechanisms produce either allergies or asthma.
- Treatment strategies for allergies and asthma are different.
- The management of one condition has little bearing on the outcome of the other.
- Lack of communication

Changes in Thinking

- Epidemiologic studies
- More emphasis was placed on the similarities between the upper and lower airways.
- A greater understanding of the central role of inflammatory mediators and the arachidonic acid pathway to both allergies and asthma.
- Overlapping roles of medications
- Primary care doctors and specialists were beginning to talk.

Unified Airway - structure

- Sinuses, turbinates, septum, larynx in the upper airway.
- Trachea, bronchi, alveoli in the lower airway.
- Different structures which share a similar respiratory mucosa.
- Similar inflammatory process with eosinophils and mast cells as the major effector cells in both allergic rhinitis and asthma.
- This unified airway could be the target organ for a systemic process

Unified Airway - function

- Warmth, humidification and filtration of air to facilitate gas exchange.
  - Oral breathing of cold air is associated with a decreased FEV₁ in patients with asthma, but this decrease could be prevented by nasal breathing.
- Pulmonary toilet and protection of the airway.
  - Materials placed in the upper respiratory tract of patients with depressed consciousness could later be recovered from the lower airway.
  - Radiolabeled allergens placed intranasally did not enter the lungs of patients with chronic rhinosinusitis and asthma.
  - Antigens less than 10 microns (cat, rodent) may penetrate the peripheral lung and alveoli.
Statistics – Allergic rhinitis
- Over 50 million Americans suffer from allergic rhinitis, and the prevalence is rising.\textsuperscript{6}
- 54.6\% of all U.S. citizens test positive to one or more antigens – 25\% are sensitized to dustmite, grass, ragweed and cockroach.\textsuperscript{7}
- Allergies are the 6\textsuperscript{th} leading cause of chronic disease in the US, costing the healthcare system $18 billion annually.\textsuperscript{8}
- 3.4 million days lost from work annually and 2 million days lost from school.
- Approximately 25 \% decline in worker productivity

Statistics - asthma
- Approximately 15 million people in the US suffer with asthma.\textsuperscript{8}
- Between 1982 and 1991, the mortality rate due to asthma rose 40\%.\textsuperscript{9}
- In that same period, self-reported asthma increased by 42\%.\textsuperscript{9}
- Hospitalization rates also on the rise.\textsuperscript{10}

Comorbidity – allergies & asthma
- Patients with allergic rhinitis are 3 X more likely to develop asthma than the general population.\textsuperscript{11}
- The prevalence of allergic rhinitis in people with asthma is 4 – 6 X higher than in the general population.\textsuperscript{12}
- Cross-sectional survey demonstrated that the risk to a child in developing allergic rhinitis, asthma or atopic dermatitis was related to the allergic disorders present in the parents.\textsuperscript{13}

Allergies & asthma on the rise
- Hygiene hypothesis
- Th1/Th2 immune switching
- Lower use of ASA in children
- Industrialization of underdeveloped countries
- Changes in the indoor living environment
- Effects of breastfeeding

Linneberg et al. Allergy 2002;57:1048-1052
- Patients with skin-positive AR
- n=734
- Ages 15-69 years old
- Followed from 1990 till 1998
- Relative Risk of developing asthma:
  - Pollen 8.2
  - Animal dander 18.9
  - Dust mite 46.5

Asthma Mortality
- 2000: 1.6 per 10,000
- This rate continues to decline
- Currently, the mortality rate for African Americans is 200\% higher than the asthma mortality for caucasians.
Pathophysiology of Asthma

- Reversible airway obstruction
- Airway inflammation
- Increased airway responsiveness to a variety of stimuli
  - URI, allergy, tobacco, cold air, emotion, exercise, GERD
- As the condition progresses, it becomes less and less reversible

Physical Exam for Asthma

- Wheezing (end expiratory)
- Coughing with tenacious mucus
- Hyperexpansion of the chest from air-trapping with hyper-resonance
- Prolonged forced expiration
- Supraclavicular retraction on inspiration
- Tachycardia and tachypnea often present
- Symptoms may not be present at the time of the exam.

Pulmonary Function Testing

- Spirometry used to plot flow/volume loops
- FEV₁ is decreased for obstructive disease, FVC is normal.
- 95% of FVC can be exhaled in 3 sec.
- Degree of obstruction:
  - 70-85% of predicted FEV₁ is mild obstruction
  - 60-69% is considered moderate obstruction
  - 50-59% is considered moderately severe obstruction
  - Less than 35% is considered very severe
- Increase of 12% of FEV₁ with bronchodilator is suspicious for asthma.
- Methacholine challenge – determine the amount needed to drop the FEV₁ by 20% (PC₂₀). In asthma, PC₂₀ is lower compared to the normal population.

Assessing Asthma Control

- Self-reported symptoms
- Limitations in activity
- Nocturnal/early morning awakenings
- Frequency of acute episodes/use of rescue inhaler
- Objective measures:
  - PFT, peak flow monitoring
  - Questionnaires (ATAQ, ACQ, ACT)
- "Level of control" is key to outcome

Pharmacology

- Corticosteroids
  - Inhaled
  - Oral
- Leukotriene modifiers
- Beta-2 agonists
  - Short acting
  - Long acting
- Antihistamines/anticholinergics
- Theophylline
- Anti-IgE treatment

Step-Wise Approach

- Step 1 – Asthma education, environmental control, fast-acting inhaler
- Step 2 – Add low dose ICS or leukotriene modifier
- Step 3 – Add low dose ICS plus LABA
- Step 4 – Add medium – high dose ICS plus LABA
- Step 5 – Oral steroid, anti-IgE
- Level of control determines movement
The association between allergies and asthma

- Direct effects – one condition is capable of directly altering the clinical course of the other
- Systemic effects – allergic rhinitis and asthma are manifestations of one or more common processes.

Direct effects

- Medical and surgical management of rhinosinusitis improves the clinical picture of asthma.
- Naso-pharyngo-bronchial reflex
- The effects of abnormal breathing on asthma.

Effects of medical management

- Inflammation from infection or allergy alters the quality of the air being inspired and the quality of the mucus coat (PND) which may affect pulmonary toilet and worsen asthma symptoms.
- Rachelefsky et al. demonstrated that 79% of children with asthma were able to discontinue bronchodilator therapy after their rhinosinusitis was medically managed.\(^{19}\)
- In addition, the PFTs in 67% of these patients normalized after medical management.

Effects of surgical management

- In adults with asthma and CRS, ESS resulted in:
  - 70% less frequent asthma
  - 65% less severe asthma
  - 75% reduction in hospitalization
  - 81% less acute care visits the following year

Effects of surgical management

- In pediatric patients (7 mo to 17 yrs) with asthma and CRS, ESS resulted in:\(^{21}\):
  - 89% reduction in chronic cough
  - 96% decrease in asthma symptoms
  - Reduction of monthly asthma exacerbations from 6.7 to 2.5
  - 79% reduction in visits to the ED

Naso-pharyngo-bronchial reflex

- Present in both human and animal models
- Nasal stimulation with chemicals, silica particles, cold air, mechanical stimulation and strong fumes produces bronchospasm
- May be blocked by anticholinergics, lidocaine, resection of nerves or ganglionic blockade.\(^{22}\)
- Afferent fibers from the pharynx and the nose (and possibly the sinuses) travel through the trigeminal nerve into the brain stem via the reticular formation.
- Synapse occurs in the dorsal vagal nucleus and efferent parasympathetic fibers travel to the bronchi via the vagus nerve.\(^{23}\)
The effects of abnormal breathing
- The nose warms and humidifies the air and traps particles.
- With CRS, oral breathing leads to the inhalation of dry, cold air and environmental pollutants.\(^{24}\)
- CRS leads to post nasal drip with thickening of the protective mucus coat and further irritation to the airway.

Systemic effects
- Similarities in tissue reactions
- The overlapping roles of medications
- Role of the bone marrow
- Response to bacterial infection

Tissue reactions
- Braunstahl et al. demonstrated that nasal provocation in allergic patients without asthma produced and influx of eosinophils into the nasal and bronchial epithelium and lamina propria.\(^{25}\)
- This was partly mediated by ICAM-1 and VCAM-1, which was found to have higher expression in both regions.

Mechanism of inflammation

Tissue reactions
- Ponikau et al. – studied 22 patients with refractory CRS. All sinus specimens demonstrated heterogenous eosinophilic inflammation, epithelial shedding and thickening of the basement membrane.\(^{26}\)
- This was similar in allergic and non-allergic subjects.
- The damage is associated with the presence of extracellular major basic protein (MBP).\(^{27}\)

Airway remodeling
Overlapping roles of medications

- Histamine and its metabolites are found in sputum, BAL and urine after allergen challenge in patient with allergies and asthma.\textsuperscript{28}
- Histamine produces dose-dependent bronchoconstriction and the degree of histamine sensitivity correlates with the severity of asthma.\textsuperscript{29}
- Antihistamines have been found to improve the symptoms of asthma, but the effect on pulmonary function is small.

Leukotrienes are 1000 times more potent than histamine in inducing a nasal allergic response.\textsuperscript{30}
- Release of leukotrienes C\textsubscript{4}, D\textsubscript{4} and E\textsubscript{4} correlated with clinical response in ragweed-sensitive patients challenged intranasally with ragweed.\textsuperscript{31}
- Leukotriene receptor antagonists have emerged as a very effective medication for the control of symptoms of allergic rhinitis.

Overlapping roles of medications

- Are they improving one condition which then leads to improvement in the other or are the medications affecting the underlying systemic causes?
- To help answer this question, we had to look in an unexpected location ...

The role of the bone marrow

- In a murine model, specific nasal challenge with allergen produced a local nasal inflammatory response along with increases in eosinophils, basophils and hemopoietic stem cells in the bone marrow.\textsuperscript{32}
- Th2 lymphocytes from nasal and sinus tissue migrate to the bone marrow where they stimulate the production and maturation of inflammatory cells.\textsuperscript{33}

Activated inflammatory cells may enter the general circulation from the sinonasal tract or the bone marrow, where they migrate to the lower respiratory tract.\textsuperscript{33}
- Where else do they go?
- So what is the role?

The response to bacterial infection

- IgE specific to staph enterotoxins A and B is found 50\% of the time in bilateral nasal polyp tissue.\textsuperscript{34}
- Staph enterotoxin IgE was demonstrated in the serum of 50\% of patients with CRS and nasal polyps, but none in control subjects.\textsuperscript{35}
- Serum IgE levels to enterotoxin are found more often in patients with asthma, and more often in severe asthma than mild asthma.\textsuperscript{36}
The association between allergies and asthma
- Likely, there is a combination of direct and systemic effects which are leading to the combined expression of allergic rhinitis and asthma in predisposed individuals.
- Some have proposed that direct effects are more active in infectious CRS, while systemic effects are more important for inflammatory CRS characterized by allergic rhinitis, sinonasal polyps, asthma and ASA sensitivity.

Conclusions
- Allergic rhinitis and asthma have been on the rise over the past 20 years.
- An increasing number of these patients suffer from both conditions.
- More focus has been placed on the similarities between the upper and lower airways, leading to the "Unified Airway Model".
- The association between allergies and ASA sensitivity.
- Inflammatory CRS characterized by systemic effects which are leading to novel treatment strategies.

Future directions
- Following the lead of the "Unified Airway", all the medical and surgical specialties must be united in their resolve to broaden their perspective beyond their own narrow region.
- Understanding the impact and relationship that systemic inflammatory processes can have on a variety of conditions will help us all serve out patients better.
- This goal can only be reached by continued research, constant communication and collaboration between and among primary care doctors and specialists.

References


References


References


