Allergy Phenotypes - Rhinitis

Carmen Rondón, MD PhD
Allergy Unit, Regional University Hospital
Málaga, Spain
Rhinitis a Complex Syndrome

Multifactorial Etiology

GENOTYPE

CLINICAL PRESENTATION

EVOLUTION

COMORBIDITIES

TREATMENT

ENDOTYPES

PHENOTYPES

CLINICAL MANAGEMENT

Rondon C. JIACI 2012
PRACTALL 2014: Phenotypes and Edotypes of Rhinitis

Phenotypes & Endotypes of Rhinitis and their Impact on Management

Nikolaos G. Papadopoulos, Jonathan Bernstein, Pascal Demoly, Mark Dykewicz, Wytske Fokkens, Peter Hellings, Anju Peters, Carmen Rondon, Alkis Togias, Linda Cox

Under elaboration

TASK FORCE (ENT SECTION) 2014: Phenotype of NAR

Non-Allergic Rhinitis: Position paper of the European Academy of Allergology and Clinical Immunology


Under elaboration
Rhinitis Phenotypes

- Phenotypes can be dynamic and overlap or may develop into one another
- Different endotype may share a same phenotype

Papadopoulos NG, et al. PRACTALL Phenotypes and Endotypes of rhinitis 2014 (under elaboration)
Rhinitis Phenotypes

- Phenotypes can be dynamic and overlap or may develop into one another
- Different endotype may share a same phenotype

Allergic Rhinitis Phenotypes

Phenotypes
Endotypes
Differential diagnose
Treatment

Papadopoulos NG, et al. PRACTALL Phenotypes and Endotypes of rhinitis 2014 (under elaboration)
Rhinitis Phenotypes

**SEVERITY**
- Mild
- Moderate
- Severe
- SCUAD

**DURATION**
- Persistent
- Intermittent
- Acute
- Chronic

**TEMPORAL**
- Seasonal
- Perennial
- Occupational

**SYMPTOMS**
- “Runners”
- “Blockers”

**CONTROL**
- Controlled
- Uncontrolled

**TREATMENT**
- “Responders”
- “Non Responders”

Papadopoulos NG, et al. PRACTALL Phenotypes and Endotypes of rhinitis 2014 (under elaboration)
Nasal Hyperreactivity

Not exclusive only idiopathic rhinitis

- **Chemical irritants:**
  - Tobacco smoke
  - Pollutants: smog, diesel, SO2, NO2, CO, CO2
  - Strong smells: perfumes, bleach, solvents

- **Physical irritants:**
  - Intense light
  - Cold dry air: VR1 vanilloid receptor
  - Hyperosmotic: pollen – osmoreceptors
  - Temperature and humidity changes

---

Staevska M, N Baraniuk. *Curr Allergy Asthma Rep* 2005
Infectious rhinitis

• Etiology:
  – Viral Rhinitis (Common cold): acute and self-limiting
  – Bacterial Rhinosinusitis
  – Fungal Rhinosinusitis

• Symptoms:
  – Discolored rhinorrea
  – Crust formation

• Duration of the disease:
  – Acute (ARS)
    • < 12 weeks and Complete resolution
  – Chronic (CRS):
    • ≥ 12 weeks and No complete resolution

Papadopoulos NG, et al. PRACTALL Phenotypes and Endotypes of rhinitis 2014 (under elaboration)
Allergic rhinitis

- Global health problem
- Affecting 400 million persons
- Countries, ethnic groups, ages
- Impairment of quality of life
- Frequent co-morbidities
- Risk factor for development of asthma
Allergic Rhinitis - IgE mediated response

Clinical symptoms:
- Itching
- Sneezing
- Watery rhinorrhea
- Nasal congestion

Allergen exposure (IgE synthesis)

Mast cell/Basophil

Allergen re-exposure

Mucosal phagocyte tissue

Lymphoid tissue
Allergic rhinitis phenotypes

Time of exposure

• Seasonal
• Perennial
• Occupational AR

ARIA Classification

Nasal localized allergic response
Absence of Systemic Atopy
Clinical symptoms suggestive of AR

Immunological characteristics

• Th2 helper inflammatory pattern
  
  Powe DG. Clin Exp Allergy, 2001
  Powe DG. Allergy, 2004
  Rondón C. J Allergy Clin Immunol 2007
  Rondón C. Allergy 2008

• Nasal production of sIgE
  
  Huggins KG. J. Lancet, 1975
  Rondón C. J Allergy Clin Immunol, 2007
  Rondón C. Allergy, 2008

• Positive response to NAPT
  
  Carney AS. Clin Exp Allergy, 2002
  Wedbäck A. Rhinology, 2005
  Rondón C. J Allergy Clin Immunol, 2007
  Rondón C. Allergy 2008
  
  Rondón C. J Allergy Clin Immunol, 2009
  López S. Clin Exp Allergy, 2010
  
  Rondón C, AAAAI 2011

Symptoms
Rhinomanometry
Acoustic Rhinometry

Inflammatory Mediators and sIgE

Cytokines (IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-12p70)
Local Allergic Rhinitis

110 LAR patients

**Persistence**
- Persistent: 91%
- Intermittent: 9%

**Severity**
- Mild: 59%
- Moderate: 36%
- Severe: 5%

**Comorbidities**
- Conjunctivitis: 70%
- Asthma: 30%
- AD: 10%
## Demographic-clinical phenotype

<table>
<thead>
<tr>
<th></th>
<th>SAR (n=270)</th>
<th>LAR (n=110)</th>
<th>NAR (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>18 ys</td>
<td>21 ys</td>
<td>36 ys</td>
</tr>
<tr>
<td><strong>Woman</strong></td>
<td>57.8%</td>
<td>78.2%</td>
<td>52.1%</td>
</tr>
<tr>
<td><strong>Family history of atopy</strong></td>
<td>37.4%</td>
<td>44.5%</td>
<td>20.8%</td>
</tr>
<tr>
<td><strong>Rhinitis Persistence</strong></td>
<td>persistent seasonal/perennial severe 59%</td>
<td>persistent perennial severe 56%</td>
<td>persistent perennial moderate 57%</td>
</tr>
<tr>
<td><strong>Seasonality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nasal symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Frequently</strong></td>
<td>itching, sneezing and watery rhinorrea</td>
<td>itching, sneezing and watery rhinorrea</td>
<td>obstruction and mucus rhinorrea</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>watery rhinorrea</td>
<td>watery rhinorrea</td>
<td>obstruction</td>
</tr>
<tr>
<td><strong>Triggering factors</strong></td>
<td>house dust pollen</td>
<td>house dust pollen</td>
<td>chemical irritants air conditioning</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td>39%</td>
<td>31%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td>62%</td>
<td>65%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Conjunctivitis</strong></td>
<td>11%</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Atopic dermatitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Onset childhood</strong></td>
<td>38%</td>
<td>36%</td>
<td>9%</td>
</tr>
</tbody>
</table>

a: NAR vs SAR p<0.05; b: NAR vs LAR p<0.05
ALLERGIC RHINITIS

ARIA Treatment Strategy

Allergen Immunotherapy

- Immune-modifying and etiologic treatment
- Safe and effective
- Symptom improvement and/or reduction of the use of rescues medication
- Long-lasting effect once discontinued
- Modify disease evolution
  - Prevention of the onset of new skin sensitizations
  - Prevention of the onset of asthma (?)
- Improvement of the quality of life

Bousquet J. Allergy 1998
Walker SM, JACI 2001
Alvarez-Cuesta E. Clin Exp Allergy 2005
Pfaar O. Allergy 2014
Allergen Immunotherapy

- Immune-modifying and etiologic treatment
- Safe and effective
- Symptom improvement and/or reduction of the use of rescues medication
- Long-lasting effect once discontinued
- Modify disease evolution
  - Prevention of the onset of new skin sensitizations
  - Prevention of the onset of asthma (?)
- Improvement of the quality of life

Could LAR patients benefit from specific Immunotherapy?

Bousquet J. Allergy 1998
Walker SM, JACI 2001
Alvarez-Cuesta E. Clin Exp Allergy 2005
Pfaar O. Allergy 2014
LAR: Allergen tolerance and immunologic changes after preseasonal SCIT-grass pollen

**Study Design:** Pilot observational study in real condition

**Study Groups:** 20 adult LAR-grass:

- SCIT group (N:10) = SCIT (6 months) + RM spring
- Control group (N:10) = RM spring

**Immunotherapy:** Aluminium-adsorbed grass mix pollen extract

**Study duration:** One year: 6 months of preseasonal SCIT

*Rondón C, JACI 2011*
Immunotherapy in LAR
6 month of preseasonal grass-SCIT

Increase of tolerance 100%
NAPT Neativization 30%

Rondón C et al., JACI 2011
DBPC Clinical Trials (Phase 2)

Efficacy of ITA in LAR


2. Efficacy of a Depigmented extract of *Phleum* in local allergic rhinitis (GRAMAL). EudraCT:2010-020949-26. **On going**
**Subcutaneous Immunotherapy with *Dermatophagoides Pteronyssinus* in LAR (ECRL1 Study)**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Interventional</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Design:</strong></td>
<td>Treatment, parallel assignment, randomized, double-blind, placebo-controlled, safety/efficacy study</td>
</tr>
<tr>
<td><strong>Enrolment:</strong></td>
<td>36 LAR patients</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>24 months</td>
</tr>
<tr>
<td><strong>Arms:</strong></td>
<td>- Active = Pangramin Plus® D. pteronyssinus 100%</td>
</tr>
<tr>
<td></td>
<td>- Placebo = Placebo</td>
</tr>
<tr>
<td><strong>Rescue medication</strong></td>
<td>Oral antihistamines</td>
</tr>
<tr>
<td>(both arms):</td>
<td>Intranasal corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Oral corticosteroids</td>
</tr>
</tbody>
</table>

ECRL1 study. NCT02123316
## PRELIMINARY RESULTS

### ALL SUBJECTS RECRUITED (N=36)

Characteristics of the subjects

<table>
<thead>
<tr>
<th>Subjects, N (%)</th>
<th>36 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>recruited</td>
<td>36 (100%)</td>
</tr>
<tr>
<td>withdrawn</td>
<td>8 (22.2%)</td>
</tr>
<tr>
<td>completed</td>
<td>28 (77.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender, N (%)</th>
<th>9 (25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>men</td>
<td>9 (25)</td>
</tr>
<tr>
<td>women</td>
<td>27 (75)</td>
</tr>
</tbody>
</table>

| Age, mean (SD) | 39 (4.8) |
Nasal allergen provocation test with DP

**Active Group**

<table>
<thead>
<tr>
<th>Improvement</th>
<th>12/18 (67%)</th>
<th>9/18 (50%)</th>
<th>3/18 (17%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase of tolerance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Improvement</td>
<td>6/18 (33%)</td>
<td>4/18 (22%)</td>
<td>2/18 (11%)</td>
</tr>
<tr>
<td>No changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease of tolerance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Placebo Group**

<table>
<thead>
<tr>
<th>Improvement</th>
<th>1/18 (6%)</th>
<th>0/18 (0%)</th>
<th>1/18 (6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase of tolerance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Improvement</td>
<td>17/18 (94%)</td>
<td>11/18 (61%)</td>
<td>6/18 (33%)</td>
</tr>
<tr>
<td>No changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease of tolerance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ECRL1 study. NCT02123316
RHINITIS MANAGEMENT

ALLERGIC

- Specific Immunotherapy
- Patient Education
- Avoidance Measures

NON ALLERGIC

- Pharmacotherapy

NO
RHINITIS

ALLERGIC

YES

Symptoms SPT sIgE

NON-ALLERGIC

NO

LAR

NOT SUFFICIENT
Nasal allergen provocation test in LAR

- Diagnosis
- Immunologic mechanism
- Clinical and immunological response to AIT
Non infectious, Non-Allergic Rhinitis

- Important health problem
- Prevalence 23-70% adults
  - 19 millions USA
  - > 200 millions worldwide

- Heterogeneous group: different phenotypes and endotypes

<table>
<thead>
<tr>
<th>PHENOTYPES</th>
<th>ENDOTYPES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic rhinitis</td>
<td>Inflammatory</td>
</tr>
<tr>
<td>NARES</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Non-allergic occupational rhinitis</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Senile rhinitis</td>
<td></td>
</tr>
<tr>
<td>Drug-induced rhinitis</td>
<td></td>
</tr>
<tr>
<td>Hormonal rhinitis</td>
<td></td>
</tr>
<tr>
<td>Gustatory rhinitis</td>
<td></td>
</tr>
</tbody>
</table>

Molgaard E. Allergy 2007; 62:1033-7
GA2LEN Review Allergy 2008;63:842-853
Rondón C. JACI 2009;123:1098-1102
Idiopathic rhinitis

Neurogenic endotype

• It is the most prevalent NAR phenotype (50-70%)
• Unknown aetiology
• Diagnosis by exclusion
• A better definition of endotypes and biomarkers is required

• Endotypes:
  - Neurogenic: NANC or peptidergic disorder, nociceptive
    TRPV1- SP signaling pathway upregulated
  - Inflammatory: controversial
NAR Treatment strategy

NAR Phenotypes

Non-allergic Senile rhinitis (>65 y)

Gustatory rhinitis

Non-allergic Occupational rhinitis

Hormonal-induced rhinitis

Non-allergic Drug-induced rhinitis

Idiopathic rhinitis

Pathophysiology

Mucosal/glandular atrophy and/or MO

Neurogenic inflammation

Neurogenic inflammation

Neuronal imbalance

Neuronal imbalance

Neurogenic inflammation and/or MO

MO = mechanism unknown

Treatment

Ipratropium bromide

Avoidance

Nasal capsaicin

Avoidance

Nasal corticosteroids

Nasal cromones ?

Avoidance

Nasal corticosteroids

Nasal capsaicin

Allergy Research Group, Regional University Hospital of Malaga

Miguel Blanca
Group Leader

Mª Jose Torres
Clinical coordination

Lina Mayorga
Research coordination

Paloma Campo
Asthma and Rhinitis

Carmen Rondon
Rhinology

Inmaculada Doña
Drug allergy

María Salas
Drug allergy

Francisca Gomez
Food allergy

Mª Isabel Montañez
Dendrimers

Enrique Gomez
T cells

Tahia Fernandez
B cells

Jose A Cornejo
Molecular Genetics

Pedro Ayuso
Molecular genetics

Xavier Leguevel
Nanoparticles

Ana Aranda
Microarrays

Adriana Ariza
Humoral Allergy

Mª Carmen Plaza
Molecular Genetics

Mª Luisa Macías
Microarrays

Miguel Gonzalez
Humoral Allergy

Lidia Menendez
Cytometry Technician

Miriam Osorio
Microarrays Technician

Veronique Godenau
Molecular Biology Technician

Luisa Galindo
ATS

Raquel Jerez
Secretary
“Clinical Cases in Allergic Rhinitis and Asthma”
28-31 August, 2014 - Malaga-Spain

HOTEL SOL PRINCIPE

Co Chairs: Carmen Rondon - Cemal Cingi

Preliminary Speakers
Carmen Rondon  Spain
Cemal Cingi  Turkey
Michael Rudenko  Great Britain
Miguel Blanca  Spain
Paloma Campo  Spain
Peter Hellings  Belgium
Philippe Gevaert  Belgium
Philippe Rombaux  Belgium
Ralph Mösges  Germany

www.c2ar.org
European Academy of Allergy and Clinical Immunology
6 – 10 June 2015
Barcelona, Spain

EAACI Congress 2015

Abstract Submission Deadline:
15 January 2015

www.eaaci2015.com
Allergic response in nasal mucosa

- Nasal mucosa → 1er line of contact Immunological System and Allergens

- IgE mediated nasal inflammatory with infiltration of Th2 lymphocytes, basophils, mast cells, dendritic cells and eosinophils

- Local synthesis of IgE: Higher proportion of B cells and plasma cells in nasal mucosa than in serum

<table>
<thead>
<tr>
<th>Allergic rhinitis</th>
<th>B cells</th>
<th>Plasma cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal mucosa</td>
<td>1/25</td>
<td>1/15</td>
</tr>
<tr>
<td>Serum</td>
<td>1/10.000</td>
<td>1/10.000</td>
</tr>
</tbody>
</table>

King CL *J.Immunol.Methods* 1990