CRS and comorbidities

Prof Dr Peter W. Hellings

University of Leuven
University of Amsterdam
University of Ghent
Comorbidities

Allergy

Immunodeficiencies

Lower airways diseases

CF and PCD

Fungal Rhinosinusitis

Vasculitis and granulomatous diseases
CRS and Allergy

3 ENTITIES

Allergic rhinitis
Central Compartment Allergic Disease (CCAD)
Allergic fungal rhinosinusitis
CRS and Allergic rhinitis

Common immune pathway in AR and subgroup of CRS
Local polyclonal IgE production in CRSwNP (also in non-atopic patients)
Allergy may aggravate CRS severity
Challenge of relative contribution of perennial allergen sensitization
Allergy is not a risk factor for CRS
Some associations between sensitization and CRS
Table 8.1.1. The association of sensitisation with CRS. Recent studies after EPOS2012.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Effect</th>
<th>Department</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benjamin et al. 2019**</td>
<td>CRSsNP, CRSwNP</td>
<td>The prevalence of atopy was 52% in CRSsNP and 76% in CRSwNP. The atopic patients had more severe radiographic disease compared with non-atopic patients in CRSsNP.</td>
<td>Tertiary Allergology Department, ENT</td>
</tr>
<tr>
<td>Shen et al. 2019**</td>
<td>CRS</td>
<td>The ImmunoCAP test was 51% positive in CRS patients. The peripheral eosinophil count in the allergic group was higher than the non-allergic group.</td>
<td>Department of Otolaryngology</td>
</tr>
<tr>
<td>Ho et al. 2019**</td>
<td>CRS</td>
<td>Positive allergen sensitization was 53% in CRS patients. Atopy was associated with younger age at the time of surgery, CRSwNP, asthma, and eosinophilic CRS. Atopy was also associated with increased severity in nasal symptom score and worse scores in the loss of smell/taste and need to blow nose questions in the CRS population.</td>
<td>Rhinology, and Skull Base Research Group</td>
</tr>
<tr>
<td>Philipott et al. 2018**</td>
<td>CRSsNP, CRSwNP allergic fungal rhinosinusitis</td>
<td>The prevalence of self-reported confirmed inhalant allergy was 13.1% in control, 20.3 in CRSsNP, 31.0% in CRSwNP and 33.3% in AFRS respectively. The self-reported house dust mite allergy was significantly higher in CRSwNP (16%) compared to CRSsNP (9%). The prevalence of self-reported aspirin sensitivity was 2.26% in control, 3.25% in CRSsNP, 9.61% in CRSwNP and 40% in AFRS respectively.</td>
<td>Population study</td>
</tr>
<tr>
<td>Hamizan et al. 2017**</td>
<td>Patients had undergone nasal endoscopy</td>
<td>Diffuse oedema and polypoid oedema demonstrated the strongest association with inhalant allergy.</td>
<td>Department of Otolaryngology-Head and Neck Surg</td>
</tr>
<tr>
<td>Li et al. 2016**</td>
<td>CRSwNP</td>
<td>Atopic patients were younger than non-atopic patients. There was no association between atopy status and either disease severity or recurrence in patients with chronic rhinosinusitis with nasal polyps.</td>
<td>Department of Otorhinolaryngology – Head and Neck Surg</td>
</tr>
<tr>
<td>Yacoub 2015**</td>
<td>CRSwNP</td>
<td>60% of patients were atopic. Patients with atopy had higher recurrence rate.</td>
<td>Allergy and Clinical Immunology Branch</td>
</tr>
<tr>
<td>Green et al. 2014**</td>
<td>CRS</td>
<td>In CRS patients, 73% had at least one of the positive allergen extracts in the skin prick test compared with 32% of the control patients with chronic idiopathic urticarial. The perennial allergy was more common than seasonal allergy in CRS.</td>
<td>Allergy and Clinical Immunology Branch</td>
</tr>
</tbody>
</table>
CRS and Allergic rhinitis

Anti-allergic treatment is recommended in those CRS patients with comorbid allergy:

- Allergen and irritant avoidance
- Pharmacotherapy
- Allergen-specific immunotherapy (AIT)
Recently described variant of CRS (since 2014)
Polipoid edematous changes of middle turbinate
Also other structures like post. septum, and sup. turbinate
High sensitization to inhalant allergen rate
Further studies need to validate the etiology and clinical course
CRS and Immunodeficiencies

Primary Immunodeficiencies
B-cell (humoral), T-cell (cellular) and/or phagocytes/compliment (innate) deficiency

Secondary Immunodeficiencies
General condition
Immunosuppressive treatment
HIV
Immunoglobuline deficiencies

up to ¼ of patients with severe or difficult-to-treat CRS

some bias in reported prevalence

some uncertainty about best approach

subtypes:

- X-linked a-gammaglobulinaemia
- Common variable immunodeficiency (CVID)
- Selective immunoglobulin A (IgA) deficiency
- Immunoglobulin G (IgG) subclass deficiency
- Selective antibody deficiency
For CRS patients suspected of having humoral immunodeficiency because of the characteristics of their presentation or their response to treatment, **measurement of serum immunoglobulin levels is the key investigation**.

If the levels are normal, but the suspicion of humoral immunodeficiency is high, referral to a clinical immunologist is optimal.

It is of paramount importance that the diagnosis and its’ implications are established in collaboration with a **clinical immunologist as some treatments are not available (isolated IgA deficiency) or may not be indicated (like IgG subclass deficiencies)**.
Immunoglobuline deficiencies

Therapy: few controlled trials

Ig replacement therapy
Prophylactic antibiotics
Pneumococcal vaccinations
(in case of low lgs to pneumococcal serotypes)
Sinus surgery
Secondary Immune deficiencies

*The prevalence of secondary immune deficiency is rising* due to the increased use of immunosuppressive agents such as rituximab (for systemic immune disorders), corticosteroids and other drugs.

**Rituximab** is a monoclonal antibody directed against CD20 that causes B-cell depletion. As the indications for rituximab are growing (auto-immune diseases) so is the incidence of rituximab-induced hypogammaglobulinaemia.
CRS and Lower airways diseases

Asthma
COPD or bronchiectasis

History
LFT
Underdiagnosis
Nasobronchial systemic and neural interaction
Global Airway Disease Concept

Health

Protection
air filtering
air conditioning
air humidification
nitric oxide production

Rhinitis
Rhinosinusitis

Trigger of inflammation
neural interaction
systemic response
epithelial dysfunction

Asthma
COPD/Bronchiectasis
CRS and Lower airways diseases

GINA and EPOS recommend
‘optimal’ treatment of both parts of the airways

Negative Impact of asthma / COPD / bronchiectasis on CRS severity and vice versa

Positive impact of CRS treatment incl. FESS on asthma / COPD / bronchiectasis
CRS and Cystic Fibrosis

Life-shortening chronic condition caused by a genetic mutation of the CFTR gene leading to defective chloride channel

<table>
<thead>
<tr>
<th>CFTR mutation classes</th>
<th>Description</th>
<th>Mutation example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>No functional CFTR being made</td>
<td>G542X</td>
</tr>
<tr>
<td>Class II</td>
<td>Incorrect trafficking of the CFTR to the cell surface</td>
<td>F508del</td>
</tr>
<tr>
<td>Class III</td>
<td>“Gating mutations” - the channels opening probability is affected</td>
<td>G551D</td>
</tr>
<tr>
<td>Class IV</td>
<td>The channels conductance is decreased</td>
<td>R117H</td>
</tr>
<tr>
<td>Class V</td>
<td>The synthesis of the channel is reduced</td>
<td>A455E</td>
</tr>
<tr>
<td>Class VI</td>
<td>The stability of the CFTR channel is decreased</td>
<td>r-delta-F508</td>
</tr>
</tbody>
</table>
CRS and Cystic Fibrosis

Bilateral nasal polyposis in children are often a clinical indication of CF(111)

Nasal polyposis in CF patients becomes more common as the children age with a prevalence of up to 50% in adolescents(112).
Key points | What’s new since EPOS 2012

1. There is a high concordance of bacteria cultured from the paranasal sinuses (based on irrigations, swabs, or mucosal biopsies) and from the lungs\(^{96}\).

2. In the western part of the world national screening programs on specific genetic disorders including CF have been implemented for newborns.


4. Ivacaftor is a gene-based therapeutic agent approved, by the US Food and Drug Administration and the European Medicines Agency for the treatment of patients with specific CF mutations. Ivacaftor is a CFTR potentiator, which increases the opening probability of the CFTR channels at the cell surface, thus increasing the flow of ions through the channel.

5. Ivacaftor has been shown to improve rhinologic QOL in patients with CF evaluated by SNOT-20.

6. Tezacaftor in combination with Ivacaftor has been approved for the treatment of patients with F508del mutations, a type II mutation.

7. The use of topical antibiotics correlates with improvement in symptom and endoscopic scoring in uncontrolled studies and is safe.

8. Some studies recommend that sinus surgery is performed in CF patients without chronic lung infection or with a transplanted lung in order to attempt to eradicate gram-negative bacteria in the paranasal sinuses, thereby avoiding or preventing re-colonisation of the lungs.
CRS and PCD

PCD = collection of rare inherited disorders that affect motile cilia, leading to deficient/absent mucociliary clearance

Whenever nasal polyps are evident on nasal endoscopy of a child the diagnosis of PCD or CF must be considered.
Conditions that support PCD diagnostic testing:

1. Situs inversus plus respiratory or nasal symptoms
2. Neonatal respiratory distress of unknown cause
3. Sibling with primary ciliary dyskinesia (PCD)
4. Daily lifelong wet cough
5. If considering testing for CF, also consider testing for PCD particularly if rhinitis, rhinosinusitis or glue ear are present
6. Unexplained bronchiectasis
7. Serous otitis media in association with lower and upper airway symptoms
8. Cardiac disease associated with heterotaxy if there is suspicion of respiratory, nasal or ear problems
CRS and PCD

Key points | What’s new since EPOS 2012

1. The number of genetic loci contributing to PCD has expanded to more than 35.
2. Diagnostic criteria now include nasal nitric oxide (nNO).
CRS and Fungal Rhinosinusitis

Fungi are ubiquitous
Fungi might be pathogens when immune responses are evoked in host
Definition and characterization of fungal rhinosinusitis is still controversial
CRS and Fungal Rhinosinusitis

Fungi and the human immune response

Allergic fungal rhinosinusitis
Fungal ball
Invasive fungal rhinosinusitis

IMMUNE HYPERSENSITIVITY
IMMUNOCOMPETENT
IMMUNE SUPPRESSION
Fungus ball

Fungus ball = collection of fungal debris usually within a single sinus

Female predisposition
Maxillary and sphenoidal sinus cavities mostly affected.

Surgery is primary treatment
Allergic Fungal Rhinosinusitis

Subset of polypoid CRS with
1/ eosinophilic mucin with non-invasive fungal hyphae and
2/ type I hypersensitivity to fungi
May account for up to 10% of CRS cases

Some controversy about AFRS being a distinct clinical phenotype of CRS
EPOS steering group decided on maintaining the definition of AFRS
Allergic Fungal Rhinosinusitis

Five **major criteria** in the original Bent-Kuhn diagnostic criteria should be met to make the diagnosis as three of the five are common in most CRSwNP

1/ Nasal polyposis
2/ Fungi on staining
3/ Eosinophilic mucin without fungal invasion into sinus tissue
4/ Type I hypersensitivity to fungi
5/ Characteristic CT scan findings: soft tissue differential densities and unilaterality or anatomically discrete sinus involvement.
Allergic Fungal Rhinosinusitis

Minor criteria include
bone erosion, Charcot Leyden Crystals, unilateral disease, peripheral eosinophilia, positive fungal culture

along with prior criteria:
characteristic eosinophil-rich allergic mucin visually or histopathologically
a positive fungal stain or culture from the sinus at surgery
the absence of immunodeficiency or diabetes
Allergic Fungal Rhinosinusitis

Unlike the management of classical CRS, the foundation of AFRS treatment is surgery.

The vast majority of clinical studies in the AFRS literature indicate that medical therapy alone is usually ineffective in alleviating symptoms and that surgical intervention, alone or in combination with medical therapy, leads to improved clinical outcomes.
Invasive Fungal Rhinosinusitis

Almost exclusively in immunocompromised patients
Fungal hyphae can be seen ‘within’ the mucosal tissue
Immunocompromised host reaction to fungi, like diabetes or haematologic malignancies

The three key principals of treatment:
Systemic antifungals therapy should be started
Patients should undergo endoscopic surgical debridement of necrotic sinonasal tissue
The patient’s immune suppression should be reduced when feasible
CRS and Vasculitis

Heterogenous nature of the condition

- Primary vs secondary
- Single vs multiple organ

Nomenclature revised and mainly based on affected blood vessel size (large, medium and small) with limited clinical applicability

ANCA-associated vasculitis include GPA (previously called Wegener’s Granulomatosis), EGPA (Church Straus S) and microscopic polyangiitis (MPA)
Table 8.7.1. Classification of vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides\(^{[299]}\)

<table>
<thead>
<tr>
<th>Vasculitis Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Large vessel vasculitis (LVV)**   | - Takayasu arteritis (TAK)  
- Giant cell arteritis (GCA)       |
| **Medium vessel vasculitis (MVV)**  | - Polyarteritis nodosa (PAN)  
- Kawasaki disease (KD)            |
| **Small vessel vasculitis (SVV)**   | - Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)  
- Microscopic polyangiitis (MPA)  
- Granulomatosis with polyangiitis (Wegener's) (GPA)  
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)  
- Immune complex SVV               
- Anti-glomerular basement membrane (anti-GBM) disease  
- Cryoglobulinemic vasculitis (CV)  
- IgA vasculitis (Henoch-Schonlein) (IgAV)  
- Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis) |
| **Variable vessel vasculitis (VVV)**| - Behcet's disease (BD)  
- Cogan's syndrome (CS)            |
| **Single-organ vasculitis (SOV)**   | - Cutaneous leukocytoclastic angiitis  
- Cutaneous arteritis Primary central nervous system vasculitis  
- Isolated aortitis  
- Others                       |
| **Vasculitis associated with systemic disease** | - Lupus vasculitis  
- Rheumatoid vasculitis  
- Sarcoid vasculitis  
- Others                       |
| **Vasculitis associated with probable etiology** | - Hepatitis C virus-associated cryoglobulinemic vasculitis  
- Hepatitis B virus-associated vasculitis  
- Syphilis-associated aortitis  
- Drug-associated immune complex vasculitis  
- Drug-associated ANCA-associated vasculitis  
- Cancer-associated vasculitis  
- Others                       |
CRS and Vasculitis

History: severe CRS including crusting, facial pain, multi-organ involvement

Positive ANCA test with raised ESR and CRP

CT scan showing bone erosion and/or thickening

Histology
Key points | What’s new since EPOS 2012

1. A low threshold of suspicion should be maintained for ANCA-associated vasculitis (granulomatosis with polyangitis (GPA), eosinophilic granulomatosis with polyangitis (EGPA)) and sarcoidosis, all of which can affect the upper respiratory tract and present with apparent chronic rhinosinusitis.

2. The ANCA test has become the mainstay of diagnosis in vasculitis but lacks sensitivity in limited forms of GPA (c-ANCA) and EGPA (p-ANCA).

3. Cocaine abuse can produce a midline destructive process which mimics GPA.

4. In GPA and EGPA systemic treatment with immunosuppression is being replaced in many cases by rituximab and other monoclonal antibodies.

5. Sarcoidosis is a chronic multi-system inflammatory disease of unknown aetiology characterised by non-caseating granuloma.

6. There is no definitive test for sarcoid other than a positive biopsy.

7. Systemic steroids remain the mainstay of treatment in sarcoidosis, though hydroxychloroquine, steroid-sparing cytotoxic agents such as methotrexate and TNF-alpha antagonists such as infliximab are being used.

8. In all these conditions, local treatment includes nasal rinsing, topical steroids and lubricants.
CRS and Comorbidities

- Allergy
- Immunodeficiencies
- Lower airways diseases
- CF and PCD
- Fungal Rhinosinusitis
- Vasculitis