Primary Immunodeficiencies and Sinusitis

Hey Jin Chong MD PhD
Assistant Professor Of Pediatrics
Children’s Hospital Of Pittsburgh
Division of Pulmonary Medicine, Allergy & Immunology

Disclosure

• none

Learning Objectives

• Recognize features of primary immunodeficiency
• Which patients should be screened and which should be referred?
• What are useful screening labs?
Primary Immunodeficiency

- More than 130 different disorders
- Affect the development and/or function of the immune system
- Overall prevalence is 1:10,000 live births
- Classified by the component of the immune system primarily involved
- Increased susceptibility to recurrent infections

Distribution of PID

[Pie chart showing distribution of PID]

Notarangelo, L. Primary Immunodeficiencies. JACI. 2010;125:S182-94

第十条警告信号

1. 四次或以上的耳鼻咽喉感染。
2. 两次或以上的严重皮肤感染。
3. 两次或以上的扁桃体感染。
4. 皮肤上有红斑。
5. 持续的扁桃体或腺体肿大。
6. 原发性或血清免疫功能异常。
7. 自发性感染。
8. 严重的病毒感染或继发性感染。
9. 严重的药物过敏反应。
10. 家族中有免疫缺陷的病史。
### Infection Pattern

<table>
<thead>
<tr>
<th>B Cells</th>
<th>T Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Bacterial, viral</td>
<td>- Bacterial, Viral, Fungal</td>
</tr>
<tr>
<td>- Otitis, sinusitis, pneumonia</td>
<td>- Pneumocystis jiroveci</td>
</tr>
<tr>
<td>- Skin abscesses</td>
<td>- Cytomegalovirus, adenovirus, RSV</td>
</tr>
<tr>
<td>- Giardia (diarrhea)</td>
<td>- Chronic diarrhea, failure to thrive</td>
</tr>
<tr>
<td></td>
<td>- Respiratory infections</td>
</tr>
</tbody>
</table>

#### Phagocytic Disorders
- Bacterial, Fungal
- Candida, Aspergillus
- Respiratory, cutaneous, abscesses, oral stomatitis
- CGD: staph aureus, serratia, Burkholderia, Nocardia

#### Complement Disorders
- C1-C3: autoimmune disorders
- C2, C3: encapsulated bacteria
- C5-C9: neisserial infection
- MBL: recurrent bacterial

Netarangelo, L. Primary Immunodeficiencies. JACI. 2010;125:S182-94

### Chronic Rhinosinusitis
- Defined as inflammation of the paranasal sinuses lasting at least 12 weeks in duration
- Immunodeficiency can make disease more refractory to standard therapies

### What PIDs should I think about?
- Humoral PID
  - Common variable immunodeficiency (CVID)
  - X-linked Agammaglobulinemia
  - IgA deficiency
  - Specific antibody deficiencies
  - IgG subclass deficiencies
Rare...

- Mannose binding lectin deficiency
- Granulomatous diseases
  - Wegeners
  - Churg-Strauss
  - Sarcoidosis

Case 1

- 11 month old male with 8 episodes of otitis media and 2 pneumonias
- Mother states he is “sick all of the time and on antibiotics”
- He had a maternal uncle die in early childhood
- He has no tonsils on exam
- IgG 30 (400-1500), IgM 10 (50-150), IgA zero

X-Linked Agammaglobulinemia (XLA)

- Described in 1952 by Colonel Ogden Bruton
- Failure of B cell precursors to mature
- 1993: Mutation in a gene responsible for development of B cells (BTK- enzyme that delivers signals to promote maturation of the B cell)
X-Linked Agammaglobulinemia

- Birth rate: 1/379,000
- 85% presented with infection
- 41% family history
- 11% neutropenia
- Average age at diagnosis with family history = 2.59 (5.37 without)

- 70% had 1 episode of otitis
- 62% had 1 episode pneumonia
- 60% had 1 episode of sinusitis
- 23% chronic/recurrent diarrhea
- 21% 1 episode of conjunctivitis


XLA

- Exam: Tonsils, adenoids and lymph nodes are small
- Labs: low IgG, IgM and IgA, low/absent B cells, absent BTK protein
- Treatment: immunoglobulin replacement, prophylactic antibiotics, generally no live virus vaccines, monitoring lung function


Case 2

- 25 y/o female with recurrent sinus infections, s/p sinus surgery
- Hospitalized 3 times in the past few years for pneumonia
- She had inflammatory bowel disease and idiopathic thrombocytopenia
- IgG 200 with undetectable IgA and normal IgM
CVID

- First reported in 1953
- Prevalence 1/25,000-200,000
- Typically diagnosed from puberty to 30 years old (should be at least 4 years old)
- Must have decreased serum of at least 2 immunoglobulins (IgG, IgM, IgA) and abnormal antibody response (lacks vaccine titers)
- Affects many organ systems
- Autoimmune disorders occur in 22% patients
- Increased risk of malignancy in the 5th-6th decade of life (GI tract and lymphoid)

Ballow, M. JACI. 2002;109:581-91

Organ systems affected in CVID

- Normal organs
  - Skin
  - Oral cavity
  - Thymus
  - Lung
  - Spleen
  - Breast
  - Retroperitoneal

- Clinical anomalies
  - Autonomic neuropathy
  - Autoimmune thyroid disease
  - Autoimmune adrenal disease (Addison’s)
  - Autoimmune anemia (AIDs)
  - Vitiligo
  - Vitiligo and alopecia


Common Variable Immunodeficiency: Clinical and Immunological Features of 248 Patients

Charlotte Cunningham-Rundles and Carol Bockman

<table>
<thead>
<tr>
<th>Associated Conditions</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections of sinuses or recurrent infections</td>
<td>242</td>
<td>90</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>108</td>
<td>27</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>105</td>
<td>41</td>
</tr>
<tr>
<td>Congenital hypothyroidism</td>
<td>58</td>
<td>23</td>
</tr>
<tr>
<td>Hematologic abnormalities</td>
<td>54</td>
<td>22</td>
</tr>
<tr>
<td>Malformations</td>
<td>53</td>
<td>21</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>49</td>
<td>20</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>42</td>
<td>17</td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>Wiskott-Aldrich</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>9</td>
<td>4</td>
</tr>
</tbody>
</table>

4/30/2014
CVID and Sinusitis

- Sinonasal symptoms were one of the most frequent initial symptoms in 36% of patients with CVID in one study

CVID-Treatment

- Immunoglobulin replacement (SC or IV)- limited data on whether or not this helps sinusitis!
- Consideration of prophylactic antibiotics
- Try inactivated vaccines but may not “work”
- Should get yearly flu shot (probably not in immunoglobulin replacement)
- Clinical f/u every 6-12 months with surveillance for autoimmune diseases and cancer

Case 5

- 8 year with recurrent sinusitis
- She also has seasonal allergies
- Labs were done that showed no detectable IgA
Selective IgA Deficiency

- Most common antibody deficiency
- Incidence of 1/400-3000
- Pathogenesis is unknown (B cells don’t make IgA)
- Serum IgA <7 mg/dL with normal IgM and normal IgG in patient older than 4
- Many individuals are asymptomatic
- Sinopulmonary infections
- Increased frequency of autoimmune disorders
- Strongly associated with atopy

Ballow, M. JACI. 2002;109:581-91

IgA deficiency and Sinusitis

- Thought that IgA prevalence may be higher in individuals with CRS compared to general population
- One study found that 6.2% of patients with CRS had IgA deficiency

Ocampo et al, Am J Rhinol Allergy 2013

Selective IgA Deficiency

- Management
  - Wear medic alert bracelet due to possibility of anaphylaxis with blood products
  - Consider prophylactic antibiotics
  - Consider immunoglobulin replacement if specific antibody deficiency
  - Monitor for development of autoimmune disease
  - Monitor for development of CVID

Specific Antibody Deficiency

- Characterized by an impaired response to immunizations with polysaccharide antigens
- Patients have normal quantitative immunoglobulins
- Most common manifestation are sinopulmonary bacterial infections with S. pneumoniae, M. Catarrhalis, H. influenzae and S. aureus
- Prevalence in general population unknown
- Treatment still remains controversial, some go on prophylactic antibiotics and a few go on IVIG—no clear data on if this is helpful or not for sinusitis

SAD and sinusitis

- In one study done at Northwestern in 129 adults who failed medical therapy and underwent FESS, they found that 73% of patients had low preimmunization protective antibody levels to pneumococcal vaccine
- When these low baseline patients were vaccinated with PPV23 and rechecked 6 weeks later, 22% did not have adequate response
- Interestingly, none had recurrent pneumonias, only 1 was on IVIG
- Concluded that patients with refractory sinusitis may have increased incidence of SAD

IgG Subclass deficiency

- IgG has 4 subclasses numbered according to serum concentration
- IgG subclass deficiency defined by having 1 or more IgG subclasses 2 SD below age-adjusted reference range, with NORMAL total serum IgG levels
- Thought that IgG1 deficiency predisposes to pyogenic airway infections
- IgG2 deficiency is most common subclass deficiency in children and thought to result in recurrent URI and LRI
- IgG3 deficiency most common in adults
- IgG4 deficiency often seen with IgG2 deficiency
IgG subclass deficiency and Sinusitis

- One retrospective study looked at 306 patients with refractory CRS: found 2% had IgG2 deficiency, 17.9% IgG3 deficiency.
- In another study looking at 245 patients with refractory CRS, 17 had IgG subclass deficiency, and 3/17 did not respond to pneumovax.
- However, Hoover et al examined 80 adults with sinusitis, and found that although 3 had IgG3 deficiency, this did NOT correlate with severity of disease.
- Others have proposed that IgG subclass deficiency is a result, not the cause of sinusitis.
- IgG subclass deficiency found in 2-20% of healthy individuals.
- 15% of normal individuals have no detectable IgG4.

So my patient has a humoral immunodeficiency, how does this affect treatment?

- For CVID - patient should be referred to an Immunologist, since there is clear evidence suggesting that IVIG prevents recurrent respiratory infections, unclear if it helps with sinusitis.
- For SAD and IgG subclass deficiency, unclear if prophylactic antibiotics play a clear role although this is often tried in a clinical setting:
  - IVIG only should be tried with history of concomitant lung infections.
  - Very few studies looking at benefit of IVIG in SAD and subclass deficiency.

Granulomatous diseases

- Churg-Strauss
- Wegeners
Churg-Strauss Syndrome

- Also known as allergic angitis and granulomatosis
- Very rare, incidence is 1-3 cases per million
- Affects ages 14-75 years old
- Pathology: necrotizing granulomatous inflammation, tissue infiltration by eosinophils, and necrotizing small vessel vasculitis
  - Characteristic lesion is “allergic granuloma”

Churg-Strauss Syndrome

- Clinically there are phases: prodromal phase where patients have asthma and AR, CRS with polyposis and recurrent rhinosinusitis
- Second phase: can occur years later, patients have peripheral eosinophilia and eosinophilic tissue infiltrates
- Third phase: systemic vasculitis symptoms of nose, sinuses, lungs and vascular system, but heart, kidneys and GI can all be involved

What criteria is needed for diagnosis of CSS? (Sinico 2009)

- Clinical criteria based on Lanham, ACR, or Chapel Hill
  - Asthma
  - Eosinophilia
  - Multi-system disease- renal, CNS, paranasal sinuses, pulmonary infiltrates
- At least one of the following:
  - Histologic proof of vasculitis
  - Positive ANCA
Churg-Strauss and Sinusitis

- In one report, 21/28 (75%) of patients had sinus involvement at onset or diagnosis
  - 2/21 were diagnosed as having CSS by an ENT
  - All patients had asthma and hypereosinophilia
  - 9 with AR
  - 3 with CRS—all improved with steroids +MTX or cyclophosphamide
  - 16 had nasal polyps
    - Of these 16, 7 underwent ESS before CSS dx made, all had early polyp recurrences
    - All pts on immunosuppressive therapy reported improvement in symptoms although they the polyposis never completely cleared

Wegener's Granulomatosis

- 3/100,000 patients
- Much more common in Caucasians
- M:F = 1:1
- Mean age of onset ~40 yrs
  - Occurs at any age
  - 15% at <19 yrs, but rare before adolescence

SIGNS & SYMPTOMS

- Pulmonary infiltrates (71%)
- Sinusitis (67%)
- Arthralgia/arthritis (44%)
- Fever (34%)
- Cough (34%)
- Otitis (25%)
- Rhinitis (22%)
Wegener’s Diagnosis

- Clinical Criteria:
  - Nasal or oral inflammation
  - Abnormal CXR showing nodules, fixed infiltrates, or cavities
  - Abnormal urinary sediment (microscopic hematuria +/- RBC casts)
  - Granulomatous inflammation on biopsy of an artery or perivascular area
  - 2+ yields sens. of 88%, spec. of 92%
- Laboratory Evaluation:
  - Leukocytosis
  - Thrombocytosis (>400,000/mm3)
  - Elevated ESR, CRP
  - Normochromic, normocytic anemia

Complications

- Renal failure
- Foot drop from peripheral nerve disease
- Skin ulcers, digital and limb gangrene from peripheral vascular involvement

Limited forms of Wegener’s

- Clinical findings that are isolated to the URT or lungs
- Occurs in ¼ of Wegener’s cases
- These patients can go on to have classic Wegeners

Limited Wegeners continued

- CRS: histopath examination of nasal and sinus tissue reveals extensive tissue necrosis and infiltration with mixed population of inflammatory cells +/- necrotizing granulomas
- Direct evidence of vasculitis rarely seen in specimens from the URT

Wegeners Nasal signs and symptoms

- Nasal crusting
- Sinus pain
- CRS
- Nasal obstruction
- Smell disturbances
- Purulent/bloody nasal discharge
- Excessive tearing
- Formation of sinus mucoceles
- They DON’T have nasal polyps
Diagnosis

- Diagnosing ANCA-associated vasculitis promptly can be life saving
  - If patient primarily has upper respiratory tract disease without other symptoms, can test for ANCA and CT scan. If ANCA positive, follow up would be needed with CBC, UA, CXR
  - Sinus biopsies are not always diagnostic

Wegeners Nasal signs and symptoms

- Patients often present with sinus infection symptoms that don’t resolve
- Over time, Wegeners can lead to nasal septal perf, saddle nose deformity, serous otitis and hearing loss
- Nasal sinus and ear involvement can present without other disease manifestations for weeks or even months before progressing to a more generalized vasculitic disease

Sinonasal Sarcoidosis

- Occurs on only 1-4% of patients with sarcoidosis
- Can have nonspecific symptoms such as recurrent sinus infections, obstruction and drainage,
- Friable mucosa with rusting and bleeding is common, unusual thickening of the nasal septum and skin findings suggestive of cutaneous lupus should clue one in to the diagnosis
Thank you