Introduction to Immunodeficiency

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Objectives

• Provide overview of common primary and secondary immunodeficiencies that present in adulthood
• Discuss basic evaluation of immune function
Outline

- Secondary immunodeficiency
- Primary immunodeficiency
  - Common variable immunodeficiency
  - Chronic granulomatous disease
  - GATA2 deficiency
  - Interferon-gamma autoantibody
A 50 year old woman with chronic kidney disease secondary to uncontrolled type 2 diabetes presents with urosepsis. She had a similar episode 2 months ago. What is the likely cause of her recurrent infections?

A. She has undiagnosed common variable immunodeficiency.
B. She has undiagnosed chronic granulomatous disease.
C. She has an enterovesical fistula predisposing her to UTIs.
D. Chronic kidney disease and uncontrolled type 2 diabetes
What are your next steps?

A. CT chest/abdomen/pelvis to assess for a potential fistula
B. Quantitative immunoglobulins, Tetanus, Diphtheria, and Strep pneumo titers
C. Dihydrorhodamine test
D. Ask your medical student to obtain a meticulous past medical and family history,
Past personal and family history is completely negative for recurrent infections. However, somebody checked quantitative immunoglobulins and titers. Total IgG is low, IgM and IgA are normal. Tetanus titer is intermediate, diphtheria and Strep pneumo titers are normal.

What is likely the cause of her recurrent episodes of urosepsis?
A. She has undiagnosed common variable immunodeficiency.
B. She has undiagnosed chronic granulomatous disease.
C. She has an enterovesical fistula predisposing her to UTIs.
D. Chronic kidney disease and uncontrolled type 2 diabetes
Secondary Immunodeficiency

- Diabetes:
  - Infections: skin infections, UTI, pneumococcal infection, pseudomonas, mucor
  - Factors: microvascular damage, neuropathy, neutrophil, T & B cell impairment
- Malnutrition
- Obesity
- Stress (trauma, surgery, burns, strenuous physical exercise, psychological)
- Protein-losing conditions (nephropathy, enteropathy) cause hypogammaglobulinemia
Immunosuppressants

- Corticosteroids: repress gene transcription of many cytokines, chemokines, adhesion molecules, inflammatory enzymes, inflammatory receptors, peptides

Immunosuppressants

• Rituximab: depletion of memory B cells
  • Long-lived plasma cells are unaffected
  • B cell recovery after treatment: 6-9 months
  • Check immunoglobulin numbers before starting therapy
  • Infection risk depends on disease process
    • Increased in lymphoma and hematologic malignancies
    • Increased in SLE
    • Increased in transplant
    • Not increased in non-SLE autoimmune conditions

• TNF inhibitors: Mycobacterial infections
A 30yo female presents to your continuity clinic with 10 days of inability to smell, facial pain, mucopurulent nasal discharge, and inability to breathe through her nose. She wants a prescription for Augmentin, which she usually receives 3-4 times/year. What are your next steps?

A. Explain that most upper respiratory tract infections are viral and there is no need for antibiotics at this time.
B. Give her the prescription.
C. Ask her whether she’s had other infections such as pneumonia or autoimmune disease, such as inflammatory bowel disease.
D. Obtain quantitative immunoglobulins and titers for tetanus, diphtheria, and Strep pneumo.
E. B, C, D
She tells you that in addition to her sinus infections, she has been hospitalized twice for pneumonia. 1 month later, she is feeling better and her lab results show very low IgG and IgA, low/normal IgM, and undetectable titers for Tetanus, Diphtheria, and Strep pneumo. What are your next steps?

A. Check HIV, B & T cell subsets, and repeat quantitative immunoglobulins  
B. Order a CT scan to look for bronchiectasis and other lung disease  
C. Order IVIG 400-600 mg/kg monthly  
D. Perform thorough review of systems  
E. Refer to Allergy/Immunology  
F. All of the above
CVID Diagnostic Criteria

• Low serum levels of
  • IgG (<400 in adults or <2.5th percentile for age)
  • AND [IgA OR IgM]
  • Impaired response to immunization
• Exclusion of all other known causes of failure of Ig production
• Age >4
Age Distribution: Continuous

<table>
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<th>Age of Onset</th>
<th>Age of Diagnosis</th>
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<td>33</td>
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<tr>
<td>Mean</td>
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<td>35.3</td>
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Presentation

- Sinopulmonary infections
  - Encapsulated organisms (H. influenzae, S. pneumococcus, Mycoplasma, Ureaplasma)
  - Recurrent and/or persistent viral respiratory tract infections

- Cytopenias

- Lung disease
  - Bronchiectasis
  - GLILD (granulomatous and lymphocytic interstitial lung disease)

- Splenomegaly, lymphadenopathy

- Granulomatous disease

- Enteropathy, inflammatory bowel disease

- Nodular regenerative hyperplasia, autoimmune hepatitis

- Lymphoma, gastric carcinoma
CVID features

- 12% cytopenia
- 7% skin
- 18% organ specific
- 9% Nodular Reticular Hyperplasia of liver
- 15% Persistent Lymphadenopathy
- 9% granuloma
- 9% infiltrative dz of small intestine (gluten-resistant)
- 3% Other Malignancy
- 3% Lymphoid Malignancy
- 3% Lymphoid Interstitial Pneumonitis
- 26% Infections Only
- 12% Persistent Lymphadenopathy

Chapel and Cunningham-Rundles. 2009.
Prognosis: Phenotyping & Immunotyping

- Decreased number of class-switched B cells (IgD-IgM-CD27+) associated with more severe phenotype (granulomatous disease, splenomegaly, autoimmunity)

Chapel 2008.
CVID: Genetics

- CVID-like conditions:
  - Hyper IgM syndrome (CD40, CD40L, AID, UNG)
  - Good syndrome ("CVID with thymoma")
  - CTLA4 deficiency
  - LRBA deficiency
  - PIK3R1 defect

- Identified genetic mutations that fall under the condition "CVID", account for 20% of CVID
  - TACI (account for 10% of CVID)
  - ICOS
  - CD19
  - CD20
  - CD21
  - CD81
  - BAFFR
Management

- Replacement Immunoglobulin (IV or SC)
- Some may benefit from prophylactic antibiotics
- Follow IgG trough levels (ideally reaching normal levels) & clinically
- DO NOT measure serological assays in individuals receiving replacement immunoglobulin, as they will reflect the antibodies present in the replacement immunoglobulin
- Response to MMR and varicella vaccines may be diminished when given to someone on Ig replacement. Recommend giving 2 weeks prior to starting replacement, or waiting 3-11 months after last dose.
- Monitor and treat autoimmune and malignant complications—sometimes with immunosuppressants!
- Consider genetic testing in those with a family history
Specific antibody deficiency

• A primary immunodeficiency of unknown origin
• Defined by:
  • NORMAL levels of IgG, IgA, IgM
  • abnormal IgG antibody to pneumococcal capsular polysaccharide
• Presentation: recurrent sinopulmonary infections
• Management depends on severity:
  • Antibiotics as needed
  • Prophylactic antibiotics
  • Replacement immunoglobulin
A 25 yo male presents with a liver abscess. Upon attempt to drain it, a “granulomatous” material is obtained. Upon further questioning, he also has a history of inflammatory bowel disease and receives antibiotics several times a year for skin abscesses. What is the most likely diagnosis?

A. Common variable immunodeficiency.
B. Chronic granulomatous disease.
C. Secondary immunodeficiency from chronic steroids needed to treat inflammatory bowel disease.
D. Just bad luck
Chronic granulomatous disease

- X-linked and autosomal recessive
- Deep-seated granulomatous infections of bacteria and fungi:
  - S. aureus, S. marsescens, B. cepacian, Nocardia spp, Aspergillus spp
  - Granulomatous abscesses of skin, lung, liver, lymph node, bone
  - Bacteremia is relatively rare
- Granulomas
- Fistulating inflammatory bowel disease
- Poor wound healing

Chronic granulomatous disease

- Defect in NADPH oxidase protein complex on the wall of the phagolysosome, leading to impaired microbial killing inside the phagolysosome
- Unclear why granulomas form

Chronic granulomatous disease

- Dihydrorhodamine test is HIGHLY sensitive and specific!

- Treatment:
  - Prophylaxis for infection: Bactrim, Itraconazole, Interferon-gamma, hematopoietic stem cell transplant
  - Steroids for granulomas and poor wound healing
  - AVOID TNF-inhibitors for inflammatory bowel disease

![Dihydrorhodamine oxidation (DHR)](image)
It’s your first day of medicine wards. You get sign-out about a 21yo female who has been in and out of the hospital for the past 9 months. She initially presented with fevers and lymphadenopathy and was diagnosed with Kikuchi-Fujimoto disease and discharged home on steroids. She presented to outside hospital with fevers, abdominal pain, diarrhea, and shock. Emergent laparotomy revealed perforated duodenal ulcers. She has been hospitalized for several months with recurrent fevers, skin ulcerations, and other complications. You look back at her numerous cultures and pathology reports and find a positive M. avium culture from several months ago. You also notice that someone performed an “immunodeficiency work-up” revealing normal numbers of IgA, IgM, IgG, negative Quantiferon gold with normal mitogen response, and very low B cell numbers.
What do you do next?

A. Order titers for S. pneumoniae, Tetanus, and Diphtheria. She could have specific antibody deficiency.

B. Order a DHR. She could have chronic granulomatous disease.

C. Send her blood to your favorite phagocyte disorder specialist at the NIH to see if she has GATA2 deficiency.

D. Perform no immunodeficiency work-up. It was complete and negative and she just has bad luck.
GATA2 deficiency

- GATA2: A transcription factor implicated in early hematopoietic, lymphatic, and vascular development
- Germline mutations arise spontaneously, and are then transmitted with autosomal dominant inheritance
- Age of onset: median age: 20 years, range: 5 months to 78 years
- Significant phenotypic variation within kindreds with the same mutation
  - E.g. 2 siblings presented at ages 26 and 19 with severe infections and malignancies. Father with same mutation was clinically silent until age 78.
- Laboratory findings:
  - B lymphocytopenia (86%)
  - NK lymphocytopenia (82%)
  - Monocytopenia (78%)
  - CD4 lymphocytopenia (51%)
  - Neutropenia (47%)
  - Normal immunoglobulins

GATA2 deficiency: Heterogeneous phenotype

Infectious (82%):

- Severe viral infections
  - Human papilloma virus (63%)
  - *Herpesvirus* (35%)
  - Molluscum contagiosum
- Disseminated non-tuberculous mycobacteria (53%)
- Other severe bacterial infections (49%)
  - Bacteremia (21%)
  - Skin and soft tissue infection (19%)
  - Pneumonia (14%)
  - Colitis (9%)
  - *C. difficile* infections
- Severe fungal infections:
  - Disseminated histoplasmosis
  - Cryptococcal meningitis
  - Invasive aspergillosis

Non-infectious:

- Pulmonary alveolar proteinosis (18%)
- Erythema nodosum
- Lymphedema (11%)
- Venous thromboses (25%)
- Aplastic anemia
- Myelodysplastic syndrome (84%)/ Acute myelogenous leukemia (14%)

Interferon gamma autoantibody

- Adult onset
- Often of Asian descent with HLA-DRB1*1602 and HLA-DQB1*0502 alleles
- Outside of Asia, most patients are female
- Present with **disseminated and bony mycobacterial infections**
- Laboratory findings:
  - Normal CD4+ cells, monocyte numbers
You diagnose a 30yo woman with lobar pneumonia. This is her second pneumonia and she also has a history of recurrent sinus infections. You suspect an antibody-mediated immunodeficiency. Her labs reveal very low IgG and IgA, low/normal IgM, and undetectable titers for Tetanus, Diphtheria, and Strep pneumo. What is the most likely diagnosis?

A. Common variable immunodeficiency
B. Specific antibody deficiency
C. Chronic granulomatous disease
A patient with the same history presents. Her labs show normal IgA, IgG, and IgM. Titers for Tetanus and Diphtheria are protective. Titers for Strep pneumonia are not protective, even 4 weeks after administering Pneumovax vaccine. What is the most likely diagnosis?

A. Common variable immunodeficiency
B. Specific antibody deficiency
C. Chronic granulomatous disease
A young man presents with a lobar pneumonia that developed into an abscess. Further history reveals recurrent skin abscesses. He also recalls the male members of his family having recurrent infections. What is the laboratory test most likely to reveal the diagnosis?

A. Quantitative immunoglobulins (IgA, IgG, IgM)
B. Specific titers to Tetanus, Diphtheria, and Strep pneumonia
C. DHR
Summary

- Secondary immunodeficiency is more common than primary immunodeficiency
- Recurrent sinopulmonary infections should prompt work-up of B-cell defect with quantitative immunoglobulins and titers of tetanus, diphtheria, and Strep pneumo.
- Recurrent abscesses, granulomas, and IBD refractory to TNF-inhibitors are suggestive of chronic granulomatous disease. DHR is highly sensitive and specific.
When should you perform immunodeficiency work-up?

• Traditionally:
  • Infections that are unusual, severe, recurrent
  • Family history of immunodeficiency

• Now, we think of immunodeficiency being a part of immune DYSREGULATION and first presentation may be:
  • Autoimmunity
  • Granulomatous disease
  • Bronchiectasis

• They can present at ANY age
• The basic “immune workup” may be completely normal.
Thank you!

Further Reading: