ANTIBODY DEFICIENCY AND AUTOIMMUNITY

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ANTIBODY DEFICIENCIES

- Common Variable Immunodeficiency (CVID)
- IgA deficiency
- X-linked Agammaglobulinemia
- Specific Antibody Deficiency
- X-linked Hyper IgM
- And many others
IG A DEFICIENCY

- most common primary immunodeficiency

- Specific lack of immunoglobulin A
  - IgA fights infections in your mucous membranes (lining of mouth and digestive tract)

- All other immunoglobulins are present/normal
  - most people look healthy
X-LINKED AGAMMAGLOBULINEMIA

- predominantly in males

- B-cell deficiency
  - --> Antibody deficiency
  - --> increased susceptibility to infections

- small to absent lymph nodes or tonsils
SPECIFIC ANTIBODY DEFICIENCY

- poor response to Pneumonia vaccine (pneumovax aka PPV23)
- normal response to conjugate vaccines (i.e. prevnar)
- normal immunoglobulin levels
**X-LINKED HYPER IGM SYNDROME**

- occurs predominantly in males

- normal to elevated IgM
  - no class switching
  - all others, IgG, A, and E are low --> frequent infections
ALL ANTIBODY DEFICIENCIES

- frequent infections
- share in propensity for autoimmunity
- We will use CVID as an example of immune deficiency and autoimmunity
QUESTIONS?
AUTOIMMUNITY IN IMMUNODEFICIENCY

- Hallmark of CVID is hypogammaglobulinemia

- However, the intrinsic dysregulation of the immune system leads to defective T-cell activation and proliferation, as well as dendritic cell and cytokine defects.

- Deficiency in one part of the immune system can lead to overcompensation in another part of the immune system leading to autoimmune disorder.
THE DILEMMA

- Immunodeficiency
  - Not enough immune response

- Autoimmunity
  - Too much immune response
Infections
Malignancies
Autoimmunity

Immune System
IMMUNE DEFICIENCY

- Malignancies
- Infections
- Autoimmunity
# Reasons for Autoimmunity

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**IMMUNE CYTOPENIA**

- The most common autoimmune conditions are immune thrombocytopenic purpura (TTP) and hemolytic anemia
- Other autoimmune complications can arise, including:
  - rheumatoid arthritis
  - pernicious anemia
  - primary biliary cirrhosis,
  - thyroiditis
  - sicca syndrome
  - systemic lupus
  - inflammatory bowel disease.
CVID AND AUTOIMMUNITY

- approximately 20% of CVID patients have an autoimmune condition

- autoimmune diseases are commonly the first manifestation of immune deficiency.
CVID AND AUTOIMMUNITY

- In one study, autoimmunity was found before the diagnosis of CVID in 17.4% of 224 patients

- In 2.3% of the 17.4% of these patients, autoimmune disease was the only clinical manifestation at the time of diagnosis of CVID.
Although males and females appear to have autoimmunity in equal numbers, there has been some geographical differences in prevalence.

Data from the recent European Society for Immune Deficiency CVID registry noted a higher prevalence of autoimmunity in the United Kingdom compared to Sweden. This suggests differences in patient referrals, environmental factors, or possibly genetic backgrounds.
DERMATOLOGIC

- Alopecia Totalis
- Vitiligo
- Psoriasis
ALOPECIA TOTALIS
VITALIGO
HEMATOLOGIC

- Immune Thrombocytopenia
- Autoimmune Hemolytic Anemia
- Autoimmune neutropenia
The most common conditions are immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA).

these occur singly or consecutively or concurrently with Evans syndrome.
IMMUNE THROMBOCYTOPENIA

Macrophage

phagocytosis

γRI, γRII

PLT

Anti-platelet antibody
AUTOIMMUNE HEMOLYTIC ANEMIA
AUTOIMMUNE NEUTROPENIA

Adapted from Fung YL et al, Vox Sang, 2011 [23]
The prevalence of ITP/AIHA is estimated to be approximately 5% to 8% in patients with CVID.

In one study of 326 CVID patients, the prevalence of hematologic cytopenias was 11% ($n = 35$): 15 with ITP, 9 with AIHA, and 11 with Evans syndrome.

Most of these patients (30 of 35) developed autoimmune disease before or concurrent with the diagnosis of CVID and start of immunoglobulin (Ig) therapy.

Autoimmune neutropenia appears to be rarer than ITP or AIHA.
ENDOCRINE

- Hypothyroidism
- Hyperthyroidism
RHEUMATOLOGIC

- Vasculitis
- Systemic Lupus Erythematosi
- Rheumatoid Arthritis
- Juvenile Rheumatoid Arthritis
- Sicca Syndrome
VASCUITIS
LUPUS
Systemic lupus erythematosus (SLE) has been described in CVID, though it appears to be uncommon.

In a review of 18 patients with CVID and SLE, 89% were females (mean age at onset of SLE, 23.8 years).

In 67% of the patients, the SLE disease activity decreased after the development of CVID. This suggests that loss of B cells or functional antibody may have contributed to clinical remission.
However, other studies have reported patients with exacerbations of SLE disease activity after development of hypogammaglobulinemia.

suggests that more than one mechanism may be involved in these two disease processes.
RHEUMATOID ARTHRITIS

Rhematic Arthritis
(Late stage)

Boutonniere deformity of thumb

Ulnar deviation of metacarpophalangeal joints

Swan-neck deformity of fingers
SICCA SYNDROME/SJOGREN’S

- Dry eyes
- Dry nose
- Dry mouth, cavities, chewing
- Dry skin
- Upset stomach
- Vaginal dryness
- Memory difficulties
- Speech difficulties
- Heartburn, swallowing
- Respiratory conditions
- Pain & arthritis
- Liver problems
- Numbness in extremities
Joint manifestations resembling rheumatoid arthritis or juvenile rheumatoid arthritis occur in 1% to 10% of patients with CVID.

These generally include symmetric involvement of few or many joints:
- commonly the knees, ankles, and hands
- may result in joint destruction.
Antinuclear antibodies or a rheumatoid factor are typically absent due to lack of antibody production in CVID.

Histologic abnormalities of the synovial membrane are unlike those seen in patients with typical rheumatoid arthritis.
Clinically, monoarticular arthritis in CVID is more commonly a result of infections such as:

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Staphylococcus aureus*

However, infections with atypical organisms such as:

- *Mycoplasma hominis, Mycoplasma pneumoniae, Mycoplasma salivarium, Ureaplasma urealyticum* are harder to diagnose

may necessitate a trial of an antibiotic to exclude such an infection
GASTROINTESTINAL

- Inflammatory bowel disease
- Primary Biliary Cirrhosis
- Autoimmune Hepatitis
- Pernicious Anemia
  - lack of intrinsic factor --> can't absorb B12 --> anemia
- Atrophic gastritis
INFLAMMATORY BOWEL DISEASE

Inflammatory Bowel Disease

Healthy

Crohn's disease

Ulcerative colitis

Fat wrapping

Muscle hypertrophy

Cobblestone appearance

Fissures

Ulceration within the mucosa
PRIMARY BILIARY CIRRHOSIS
AUTOIMMUNE HEPATITIS
Pernicious anemia is another autoimmune disease noted in a small percentage (1% to 9%) of almost all series of patients with CVID.
Inflammatory bowel–like disease has been described in 6% to 10% of patients with CVID.

Liver disease with persistently elevated liver enzymes, including primary biliary cirrhosis and what appears to be autoimmune hepatitis, has also been observed.
LIVER ENZYME ELEVATION

- In a survey of 10 CVID patients with elevated liver enzymes, biopsies demonstrated chronic inflammation.

- Four patients showed small numbers of scattered portal and/or lobular granulomas.

- Three of the patients had a coexisting diagnosis of sarcoidosis.
TREATMENT - FOR AUTOIMMUNITY

- high-dose immunoglobulins
- corticosteroids
- selected immunosuppressants, and other immune modulators.
Autoimmunity in people with Antibody Deficiencies is not uncommon

Diagnostic laboratory maybe not be helpful due deficient antibody production

Treatment for all antibody deficiencies is IV immunoglobulin (IVIG)

Treatment for autoimmune disorders can include high dose IVIG in addition to immunosuppressants as well as other modulators
SPECIAL THANKS

- Robert W. Hostoffer, DO
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QUESTIONS?