Common Variable Immunodeficiency - Co-morbid Conditions

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Mark Ballow: Disclosures

- I have a financial relationship or interest related to the content of this CME program with the following entities:
  - Talecris Biotherapeutics – advisory board
  - CSL Behring - advisory board
  - Baxter – advisory board
  - Grifols – PI phase 4 IVIG study; consultant
- Unlabeled or investigational products will not be discussed

Learning Objectives

At the conclusion of this session, the participant should be able to:

Become aware of how therapeutic decisions will affect the management of patients with CVID over the course of their lifetime.

Make more effective treatment decisions when managing complications in patients with CVID.

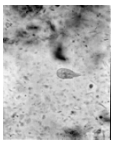
Common Variable Immunodeficiency (CVID)

- Recurrent sinopulmonary infections with encapsulated organisms
- Most common B-cell immune deficiency
  - 1:25,000 to 1:50,000
- Variable onset of clinical findings
  - Often delayed diagnosis by 6-8 yrs
- Low serum IgG, IgA, IgM
  - At least 2 Ig isotypes that are >2 SD below normal for age
  - Poor or absent specific antibody production
  - Diagnosis after age 4 to exclude transient delayed hypogammaglobulinemia of infancy (THI)
- Most common PIDD requiring therapy (IVIG)
- 50% share a common HLA haplotype
  - Families have individuals with both CVID and IgA deficiency
- Immunologically heterogeneous disorder

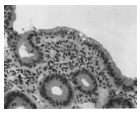
Cunningham-Rundles C, Bodian C. *Clin Immunol*. 1999;92(1):34-48.

Clinical Findings in CVID

Giardia lamblia infection

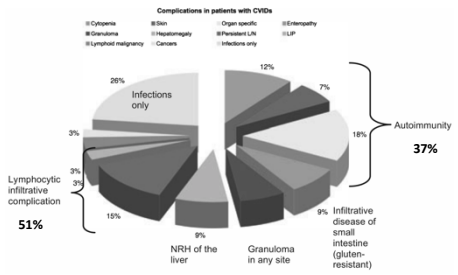


Celiac disease



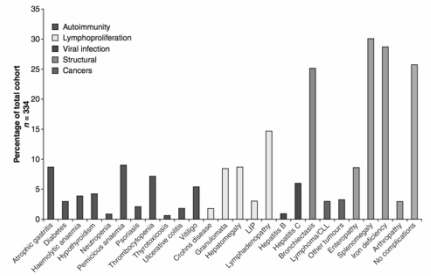
- Recurrent sinopulmonary tract infections (73%)
  - Encapsulated organisms
  - Mycoplasma
- Recurrent GI symptoms, chronic GI infection
  - Campylobacter/Salmonella
  - 10% liver disease
- 1/3 develop lymphoproliferative disorder.
  - Intestinal nodular lymphoid hyperplasia,
  - Splenomegaly
- Autoimmunity (~25%): PA, celiac disease, ITP, AIHA, systemic rheumatic disease
- Subgroup of CVID have defects in T-cell function
- Increased incidence of lymphoma (NHL) and gastric cancer

Medical Complications in Patients With CVID



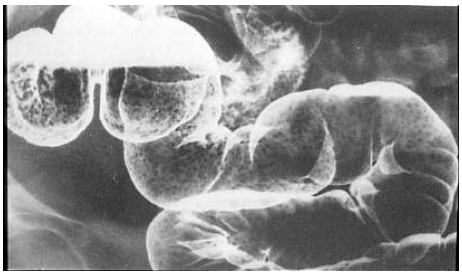
Chapel H, Cunningham-Rundles C. *Br J Haematol*. 2009;145(6):709-727.

Complications Associated With CVID



Chapel H, Cunningham-Rundles C. *Br J Haematol*. 2009;145(6):709-727.

Chronic Diarrhea in a 32-year-old Woman



Gastrointestinal Issues

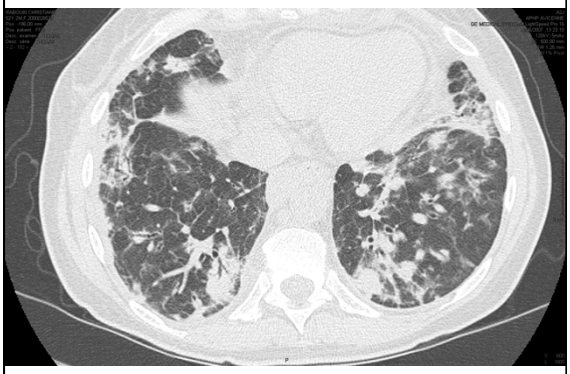
- Survey of 248 CVID patients – 21% had significant GI disease[1]
  - Often present with chronic diarrhea and malabsorption
  - Liver disease in 12%
    - Biliary cirrhosis
    - Autoimmune hepatitis
    - Nodular regenerative hyperplasia – portal hypertension and cholestasis
  - Overgrowth of small bowl with pathogens
    - *Giardia lamblia*
    - Yersinia, Campylobacter, *C difficile*, *Salmonella*
    - Chronic viral enteritis
      - Enteroviruses
      - CMV
  - Autoimmune GI problems
    - Celiac
    - Inflammatory bowl disease

1. Cunningham-Rundles C, Bodian C. *Clin Immunol*. 1999;92(1):34-48.

Gastrointestinal Management

- No lake swimming (*Giardia lamblia*)
- Stool studies
  - Reducing substances – lactose intolerance
  - Cultures –
    - request special cultures for Yersinia/ Campylobacter
    - O&P
- Liver function tests
- GI procedures
  - Imaging
    - NLH
  - Endoscopy
  - Biopsies
    - Celiac disease
    - IBD
- Nutrition support
  - Diet
  - Vitamins

Cunningham-Rundles C. *Blood*. 2010;116(1):7-15.



Pulmonary Findings in CVID

- Bronchitis/bronchiectasis
  - Serum IgG level at diagnosis does not predict subsequent pneumonias or bronchiectasis
- Granulomatous lung disease
  - 8%-12% of patients
  - May be diagnosed years before the hypogglobulinemia
    - Well-formed, non-caseating granuloma with epitheloid giant cells
    - Often misdiagnosed as sarcoid
  - Lung (54%); lymph nodes and spleen (43%); liver (32%)
  - Autoimmune disorders are commonly associated (54%)
    - Autoimmune thrombocytopenia, hemolytic anemia most common
    - Have low number of switched memory B cells

Ardeniz O, Cunningham-Rundles C. *Clin Immunol*. 2009;133(2):198-207.
Chapel H et al. *Blood*. 2008;112(2):277-286.
Mechanic LJ et al. *Ann Intern Med*. 1997;127(8 Pt 1):613-617.

Pulmonary Findings in CVID (cont'd)

- Lymphoid interstitial pneumonia (LIP)
  - Lymphoma
- Granulomatous lymphocytic interstitial lung disease (GLILD)
  - HHV8
  - Poorer prognosis, T-cell deficiency, B-cell lymphoproliferative disease
    - Median survival - 13.7 yrs vs. 28.8 yrs
    - MALT

Wheat WH et al. *J Exp Med*. 2005;202(4):479-484.
Bates CA et al. *J Allergy Clin Immunol*. 2004;114(2):415-421.

Pulmonary Disease Management

- Baseline high-resolution chest CT
  - Chest x-rays
  - Spirometry
- If lung disease present:
  - Sputum cultures/sensitivities
  - Spirometry – DLCO
  - Pulmonary care
  - Biopsies
    - Flow cytometry
    - Clonality for MALT

Pulmonary Disease Management (cont'd)

- Therapy
  - Bronchiectasis
    - Adequate IVIG/SCIG replacement therapy
    - Prophylactic antibiotics
    - Pulmonary toilet
  - Granulomatous disease
    - Oral steroids/inhaled corticosteroids
    - Hydroxychloroquine
    - TNF inhibitors

Hatab AZ, Ballas ZK. *J Allergy Clin Immunol*. 2005;116(5):1161-1162.
Lin JH et al. *J Allergy Clin Immunol*. 2006;117(4):878-882.

Clinical Findings in CVID: Autoimmune Disease

- Approximately 20%-30% have autoimmune disease
  - Diminished switched memory B cells
  - Most common hematologic (11%)
    - Rx IVIG/steroids
    - Rituximab
    - Avoid splenectomy
  - Rheumatologic
  - Endocrine
  - Pernicious anemia
    - Secondary neurologic deficits – B12 deficiency

Cunningham-Rundles C. *Blood Rev*. 2002;16(1):61-64.
Wang J, Cunningham-Rundles C. *J Autoimmun*. 2005;25(1):57-62.
Sève P et al. *Medicine (Baltimore)*. 2008;87(3):177-184.

Lymphoid Tissues

- Lymphoid hyperplasia (20%)
  - Cervical, mediastinal, abdominal
  - Biopsies
    - Reactive lymphoid hyperplasia
    - Granulomatous disease
    - Rule out lymphoma
      - Flow cytometry for tumor markers
      - Clonality by molecular analysis
      - EBV genome
- Hepatosplenomegaly
  - Secondary cytopenias – Evans syndrome
  - Liver disease
    - Autoimmune hepatitis
    - Nodular regenerative hyperplasia
      - Liver function testing

Sander CA et al. *Am J Surg Pathol*. 1992;16(12):1170-1182.
Gompels MM et al. *Clin Exp Immunol*. 2003;134(2):314-320.
Cunninham-Rundles C et al. *Am J Hematol*. 2002;69(3):171-178.
Gathmann B et al. *Clin Exp Immunol*. 2009;157(Suppl 1):3-11.

Cancer: Clinical Findings in CVID

- Malignancies
  - 2%-8% Non-Hodgkin lymphoma
    - More common in the 4th-7th decade of life
    - Female preponderance
    - B-cell type, EBV negative
    - Location in mucosal regions (marginal zone)
    - Associated with lymphoid hyperplasia, granulomatous disease, and elevated serum IgM
  - Gastric cancer
    - May be associated with *Helicobacter pylori*

Zullo A et al. *Gut*. 1999;45(1):77-81.
Mellemkjaer L et al. *Clin Exp Immunol*. 2002;130(3):495-500.
Cunningham-Rundles C et al. *J Clin Immunol*. 1987;7(4):294-299.
Cunningham-Rundles C et al. *Am J Hematol*. 2002;69(3):171-178.

Immune Defects in CVID- a Heterogeneous Disorder

- T-cell defects
  - Decreased activation and proliferation
  - Reduced numbers of peripheral blood T-cell subsets
  - Impaired cytokine production
  - Reduced expression of CD40L
  - Increased immunoregulatory T-cells
- B-cell defects
  - Reduced number of circulating B-cells
  - Defective up-regulation of CD86
  - Reduced somatic hypermutations
  - Lack of class-switched memory B-cells

Clinical Phenotypes and Biomarkers

- Clinical biomarkers
  - Poor T-cell function
  - Low B-cell numbers
  - Switched memory B cells
  - Reduced Treg
  - Very low $CD21^{+}$ B cells
  - High serum levels of BAFF and April
  - Genetic markers
    - Heterozygous mutations/polymorphisms in *TNFRSF13B* (TACI)
      - Develop autoimmunity and lymphoid hyperplasia

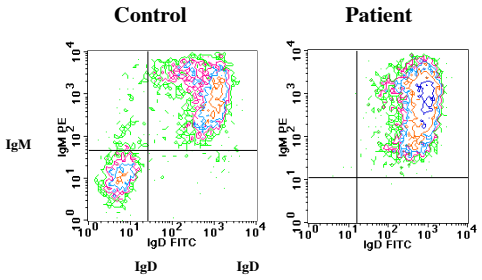
Malphettes M et al. *Clin Infect Dis.* 2009;49(9):1329-1338.
Ko J et al. *Clin Immunol.* 2005;116(1):37-41.
Alachkar H et al. *Clin Immunol.* 2006;120(3):310-318.
Knight AK et al. *Clin Immunol.* 2007;124(2):182-189.
Salzer U et al. *Blood.* 2009;113(9):1967-1976.

Switched Memory B-cells in CVID

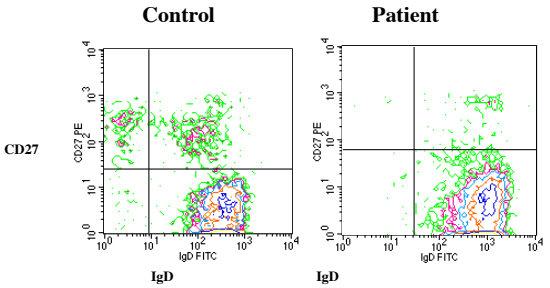
- Switched memory B-cells -
  - CD27+ IgM- IgD-
  - Group I <0.4% vs. group II >0.4%
- Patients with higher numbers (Group II) of switched memory B-cells had higher serum levels of immunoglobulins and better antibody responses to pneumococcal vaccine
- Patients in group I with low class switch memory B-cell had more autoimmmune disease
  - Poorer antibody production to polysaccharide antigens
  - More bacterial pneumonias and bronchiectasis

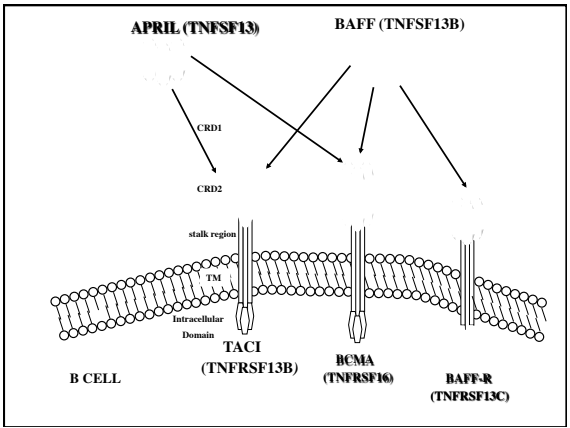
Carsetti et al JACI 2005

Flow Cytometric Evaluation -CVID



Flow Cytometric Evaluation -CVID

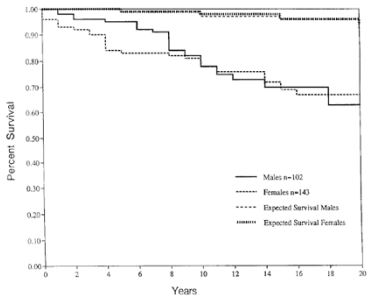




Gene Defects in Common Variable Immune Deficiency (CVID)

- Recent findings have identified specific B cell and T cell genetic defects associated with CVID
  - TACI (Transmembrane Activator and CAML Inducer) deficiency: ~10% CVID
  - BAFF (B-cell Activating Factor) receptor deficiency: uncommon
  - CD19 deficiency: uncommon
  - ICOS (Inducible COstimulator of activated T cells) deficiency
    - impaired T cell help (uncommon)

Survival Curve for Patients With CVID 1973 to 1998



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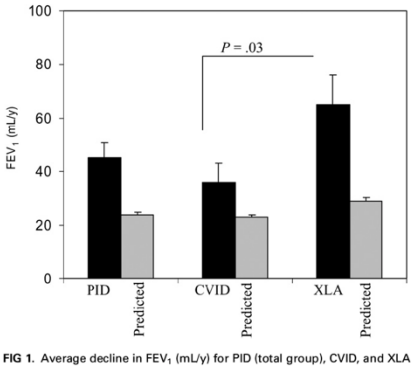
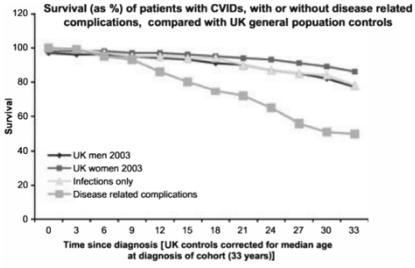


FIG 1. Average decline in FEV_1 (mL/y) for PID (total group), CVID, and XLA

Chen Y et al. *J Allergy Clin Immunol*. [Published online May 6, 2011]

Survival in Patients With CVID



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