CVID: An evolving story

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Mount Sinai School of Medicine
New York City, New York

Topics

• Defining CVID
• Does it matter what you call it?
• Phenotypes, complications and morbidity
• Laboratory markers
• Genetic tests
• Treatment?
• Inflammatory disease
• But why?
Absence of Serum Gamma Globulins in an Adult

Jay P. Sanford, M.D.,‡ Cutting R. Favour, M.D.,‡ and Melvin S. Tribeman, M.D.§

Boston

Figure 1. Various Infections and Hospitalizations in a Patient with Agammaglobulinemia.

Coming soon: next update from the IUIS committee

IUIS Classifications

1. Immunodeficiencies affecting cellular and humoral immunity
2. Combined immunodeficiencies with associated or syndromic features
3. Predominantly Antibody Deficiencies
4. Diseases of Immune Dysregulation
5. Congenital defects of phagocyte number or function
6. Defects in Intrinsic and Innate Immunity
7. Auto-inflammatory Disorders
8. Complement Deficiencies
9. Phenocopies of Inborn Errors of Immunity
## IUIS Classifications

1. Immunodeficiencies affecting cellular and humoral immunity
2. Combined immunodeficiencies with associated or syndromic features
3. Predominantly Antibody Deficiencies
   - Severe Reduction in All Serum Immunoglobulin Isotypes
   - Severe Reduction in at Least 2 Serum Immunoglobulin Isotypes with low or nl B cells
   - Severe Reduction in IgG and IgA with Normal/Elevated IgM Isotype, Light Chain, with Normal Number B Cells
4. Diseases of Immune Dysregulation
5. Congenital defects of phagocyte number or function
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### ESID workshop criteria for CVID

At least one of the following:
1. increased susceptibility to infection
2. autoimmune manifestations
3. granulomatous disease
4. unexplained polyclonal lymphoproliferation
5. affected family member

AND marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2SD of the normal levels for their age);

AND at least one of the following:
1. poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination where defined
2. low switched memory B cells (<70% of age-related normal value)

AND secondary causes of hypogammaglobulinaemia have been excluded
AND diagnosis is established after the 4th year of life (but symptoms may be present before)
AND no evidence of profound T-cell deficiency, defined as 2 out of the following (y = year of life):

1. CD4 numbers/microliter: 2-6y <300, 6-12y <250, >12y <200
2. % naive CD4: 2-6y <25%, 6-16y <20%, >16y
1. A marked decrease of IgG (at least 2 SD below the mean for age)

2. A marked decrease in at least one of the isotypes IgM or IgA,

3. Onset of immunodeficiency at greater than 2 years of age

4. Absent isohemagglutinins and/or poor response to vaccines

5. Defined causes of hypogammaglobulinemia have been excluded


CVID: improved long term survival

70% mortality after 12 years

Mount Sinai Data: Kaplan-Meier overall survival curves.

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Presence of complications

Kaplan Meier Plot of Survival by Presence of Complications

P = .0001

Resnick et al, Blood: 2012
### Fully Adjusted Cox Proportional Hazards Modeling of Complications as related to mortality.

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*Resnick et al, Blood: 2012*

### Typical patient with infections only: Bacterial pneumonia and empyema

- **42 year old lawyer** with second episode of pneumonia in 2 years; developed empyema. 
  *S. pneumonia* was cultured. Required prolonged chest tube drainage and Decortication.

**IgG = 54; IgA = 1; IgM = 4**
Phenotypes in CVID


Complications in 473 CVID subjects from MSSM

Resnick et al Blood 2012
Four patients, similar phenotype: Interstitial Lung disease

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*Fully Adjusted Cox Proportional Hazards Modeling of Complications as related to mortality.

Resnick et al, Blood: 2012
Increased mortality in subjects with ILD and lung impairment

Bronchiectasis

Impaired Lung Function

Systemic granulomatous Disease - 8 to 20%
Systemic granulomatous Disease - 8 to 20%

- cutaneous
- Bone marrow
- spleen
- Abdominal

Pulmonary lymphoid hyperplasia is the common pathology

Follicular Bronchiolitis  Lymphocytic Interstitial Pneumonitis

- Nodular Lymphoid Hyperplasia
- Granulomatous inflammation

Tertiary lymphoid structures are a feature of CVID ILD

**Patient 1**

- CD20: B cells
- Ki67: Proliferation
- Bcl6: Germinal Center
- CD23: Follicular Dendritic Cells

**Patient 4**

- CD20
- CD10
- CD3

**Patient 5**


CVID ILD is part of generalized immune dysregulation

Bronchiectasis was found in 1/3rd of patients with CT evidence of ILD (5 or more pulmonary nodules, ground glass opacity)

ILD results from immune dysregulation
- present at diagnosis in most cases
- younger CVID patients
- monogenic “CVID-like” disorders (CTLA-4 haploinsufficiency, LRBA def., PI3Kdelta and STAT3 gain-of-function)

<table>
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<tr>
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<th>No ILD</th>
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<tr>
<td>Patients, n</td>
<td>39</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>History of pneumonia</td>
<td>22 (56)</td>
<td>14 (64)</td>
<td>.78</td>
</tr>
<tr>
<td>Splenomegaly/splenectomy</td>
<td>24 (63)</td>
<td>2 (9)</td>
<td>&lt;.0001</td>
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<td>AIHA/ITP</td>
<td>22 (56)</td>
<td>1 (5)</td>
<td>&lt;.0001</td>
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<tr>
<td>Liver disease</td>
<td>8 (21)</td>
<td>0 (0)</td>
<td>.042</td>
</tr>
<tr>
<td>Enteropathy</td>
<td>4 (10)</td>
<td>2 (9)</td>
<td>1.00</td>
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CVID: 28% with Autoimmune diseases

- ITP
- Evans
- AHA
- RA
- Anti-IgA
- SLE
- Alopecia
- Diabetes mellitus
- IBD
- Pernicious anemia
- Myasthenia
- Neutropenia
- primary biliary cirrhosis
- Urticaria
- Anti cardiolipin
- JRA
- Uveitis
- Vasculitis
- Lichen planus
- Thyroid
- Vitiligo

Serum IgM level correlates with ectopic germinal centers

**B cells**
CD20

**Follicular Dendritic Cells**
CD23

**T cells**
CD3

**Germinal Center**
Bcl6

**Proliferation**
Ki67

**GC:IgM Correlation**

![Graph showing the correlation between serum IgM levels and the number of GCs. The Pearson's correlation coefficient (r) is 0.69.](image)

Serum IgM (mg/dl) vs. # of GCs
Knight et al, 2008

GI problems 915/1472 (62%) CVID subjects in the USIDNET Registry with
Infections

- H Pylori
- Giardia
- Salmonella
- Campylobacter
- Cryptosporidia
- Cytomegalovirus
- Norovirus
- Bacterial overgrowth

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Resnick et al, Blood: 2012
Increased mortality in GI disease

Resnick et al, Blood: 2012

55 CVID patients with enteropathy (MSSM)

- 29 females and 26 males.
- Mean age diagnosis of CVID was 32 years (range 2-74 years)
- Mean IgG 232 mg/dl (range 0-540), IgA 17 (0-155), IgM 43 (0-400)
- 23.6% also had autoimmune disease
- 19 had died
- Mean age of death was 44 (22-77)
- Median years from diagnosis to death was 11 (range 1-29)
- Three subjects had previously had stomach, breast and testicular cancer. Two had lymphoma; one had Hodgkin’s disease
Loss of mucosal plasma cells

Endoscopic views and pathology

- Nodular hyperplasia
- Lymphocytic infiltrate; villous atrophy
**Lymphocytic infiltrates**

- CD3 total T cells
- CD4 helper T cells
- CD8 "suppressor" T cells
- CD20 B cells

**Laboratory Markers?**
## Laboratory Differences in CVID cohorts (n = 91)

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<th>Complications n=47</th>
<th>No Complications n=44</th>
<th>*P-value</th>
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<tr>
<td><strong>Age</strong></td>
<td>42 yrs (32-49.5)</td>
<td>43 yrs (38.8-55.8)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>IgG</strong></td>
<td>207.5 mg/dl (94.3-341.5)</td>
<td>202 mg/dl (67.5-352.8)</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>IgA</strong></td>
<td>7 mg/dl (0-15.5)</td>
<td>8 mg/dl (6.0-20.5)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>IgM</strong></td>
<td>18 mg/dl (6.5-46.0)</td>
<td>22 mg/dl (12-40)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>B cell%</strong></td>
<td>7%</td>
<td>9.5%</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Isotype switched memory B cells</strong></td>
<td>0.65%</td>
<td>1.3%</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Absolute Lymphocyte</strong></td>
<td>1100 (800-1600)</td>
<td>1300 (1100-3100)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>T cells</strong></td>
<td>75%</td>
<td>75%</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>CD4+ T cells</strong></td>
<td>581 (513-816)</td>
<td>579 (336-708)</td>
<td>0.5</td>
</tr>
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*Mann-Whitney 2-tailed test

### 20 year old: IgG 168 mg/dl; IgA = 10, IgM = 24. Infections only

| CD19+ % of total lymphocytes | 11.7 % | 2.6-17.4 |
| CD20+ % of total lymphocytes | 11.8 % | 3.2-14.6 |
| CD27+ % of CD19+ B cells | L 4.8 % | 6.3-82.8 |
| CD27+ IgM+ IgD+ % of CD19+ B cells | 2.7 % | 1.7-29.3 |
| CD27+ IgM- IgD- % of CD19+ B cells | 0.5 % | 2.3-26.5 |
| CD27+ IgH+ IgD- % of CD19+ B cells | 0.3 % | 0.0-5.3 |
| IgM % of CD19+ B cells | H 88.6 % | 26.0-78.0 |
| CD38+ IgM+ % of CD19+ B cells | L 2.9 % | 4.1-42.2 |
| CD38+ IgM- % of CD19+ B cells | 31.6 % | 1.2-50.7 |
| CD21+ % of CD19+ B cells | 96.8 % | 92.1-99.6 |
| CD21- % of CD19+ B cells | 3.4 % | 0.2-6.6 |
| CD19+ | 151.2 cells/mCL | 90.0-539.0 |
| CD20+ | 152.5 cells/mCL | 95.0-580.6 |
| CD27+ | L 7.3 cells/mCL | 10.0-145.0 |
| CD27+ IgM+ IgD+ | 5.6 cells/mCL | 4.0-85.0 |
| CD27+ IgM- IgD- | L 0.8 cells/mCL | 7.0-61.0 |
| IgD+ | 0.5 cells/mCL | 0.0-12.0 |
| CD18+ IgM+ | 127.3 cells/mCL | 37.0-327.0 |
| CD21+ IgH+ | 47.8 cells/mCL | 2.0-119.4 |

**TACI** expression on B cells no reference range established

**BAFF-r** expression on T cells no reference range established
20 year old: IgG 168 mg/dl; IgA = 10, IgM= 24. Infections only

The percent of patients with selected complications is highly correlated to the numbers of switched memory B cells

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<th>Complication</th>
<th>% Switched Memory B Cells</th>
<th>P-value</th>
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<tr>
<td>Granuloma</td>
<td>&gt;0.55, ≤ 0.55</td>
<td>0.002</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>&gt;0.55, ≤ 0.55</td>
<td>0.007</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>&gt;0.55, ≤ 0.55</td>
<td>0.009</td>
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P=0.002 log-rank test
P=0.007 log-rank test
P=0.009 log-rank test
Very low or absent B cells

More than one member in a family

Severe inflammatory/autoimmune disease

Early onset, under age 10

Whole exome studies: Selectively Chosen subjects

44 Causative genes identified in 132 CVID subjects

--- genes other than TACI (32 subjects)

TACI
NFKB1
CTLA4
STAT3
KMT2D
CXCR4
PI3KCD
LRBA
STXB2
PI3KR1
LIGASE 4
IKZ1
DNA LIG1
BLK
TLR7
BACH2
E2A

TACI
NFKB1
CTLA4
STAT3
KMT2D
CXCR4
PI3KCD
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STXB2
PI3KR1
LIGASE 4
IKZ1
DNA LIG1
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TLR7
BACH2
E2A
IUIS Classifications

1. Immunodeficiencies affecting cellular and humoral immunity

2. Combined immunodeficiencies with associated or syndromic features Ligase 1, Ligase 4, KMT2D

3. Predominantly Antibody Deficiencies
   - Severe Reduction in All Serum Immunoglobulin Isotypes E2A; PIK3R1
   - Severe Reduction in at Least 2 Serum Immunoglobulin Isotypes with low or nl B cells NFKB1, IKZF1; PIK3CD
   - Severe Reduction in IgG and IgA with Normal/Elevated IgM CD40L
   - Isotype, Light Chain, with Normal Number B Cells

4. Diseases of Immune Dysregulation STXBP2; CTLA4; LRBA; BACH2

5. Congenital defects of phagocyte number or function

6. Defects in Intrinsic and Innate Immunity; TLR7; CXCr4

7. Auto-inflammatory Disorders

8. Complement Deficiencies

9. Phenocopies of Inborn Errors of Immunity

Universally impaired somatic hypermutation

Bone marrow

Lymph node

19 year old girl with progressive lung disease and enteropathy

- Lymphocytic infiltrates
- Foci of bronchiolitis obliterans
- No organisms
- Mixed T and B cell infiltrate with lymphoid nodules
- Reactive germinal center changes with mitotic figures
- Probable non caseating granuloma
- Rare giant cells

IgG = 594; IgA < 5, IgM normal
GI biopsy: villous atrophy
19 year old girl with progressive lung disease and enteropathy

- Lymphocytic infiltrates
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CTLA4: c.56_57insCTGG:p.T19fs

35 year old woman with autoimmunity and liver disease

- Frequent infections, diagnosed with CVID started on IVIg.
- IgG = 20; IgA < 4; IgM < 5
- Immune thrombocytopenia
- Splenectomy;
- Granulomatous autoimmune hepatitis
- Prednisone; methorexate =
- Liver re-biopsied: Cell Cept + prednisone
- Bronchitis, sinusitis continue; asthma diagnosed:
- CD3 = nl; CD4 = low CD8 = increased, CD56 = high; CD19 = very low
- Liver infiltrate: oligoclonal T cell population
- Died of liver and lung failure age 39
**35 year old woman with autoimmunity and liver disease**

- Frequent infections, diagnosed with CVID started on IVIg.
- IgG = 20; IgA = <4; IgM = <5
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**LRBA:** exon11: c. A1399G: p. M467V
**LRBA:** exon57: c. C8351G: p. A2784G

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**41 year old man with known CVID since age 20**

**PET SCAN**

History of ITP at age 11
IgG = 50; IgA = 0; IgM = 2; B cells 0.1%
On IVIG
C/O diarrhea and giardia isolated
Refractory to treatment with metronidazole
Abdominal pain and obstruction
CT showed a mass
PET scan = lymphoma
IgA + Plasmablastoid lymphoma/jejunum
Extensive chemotherapy,
Expired

**PIK3CD:** exon13: c.T1558G: p.S520A
Treatment

- Optimize Ig
- Steroids
- Rituximab
- Hydroxychloroquine
- Azathioprine, 6MP
- Cell Cept
- Sirolimus, everolimus
- Avoid splenectomy
- New agents: TNF inhibitors; abatacept; vedolizumab; tocilizumab

Rituximab for Cytopenias in CVID: responses

Gobert, et al. BJH, Oct 2011
What next?

1. Inflammatory Disease in CVID: why? Just the loss or regulatory genes?
2. Role of innate lymphoid cells in inflammatory disease?
3. Other causes?

Interferon signature in inflammatory complications in CVID

Park et al, PLOS 2013
CyTOF to identify cellular subsets on blood

Circulating ILC increased in CVID patients with inflammatory complications

Lineage cells: CD1d, CD3, CD11c, CD14, CD123, CD19, TCR-γδ
Lung Biopsy Samples
Inflammatory conditions in CVID have been called “Non-infectious” complications.

But are they promoted and/or sustained by microbial infections that cannot be eliminated due to the defective immunity?

1. CVID: an immune syndrome due to many causes
2. More of a pure B cell defect in some
3. Inflammatory phenotypes in 30-50%
4. Lymphoid and granulomatous expansion as a reflection of inflammatory drive
5. Innate lymphoid cells as a deleterious compensation?
6. Drivers of inflammation?
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- PJ Maglione, MD, PhD
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- Adrian Ting, PhD

Yale University
- Eric Meffre PhD

Rockefeller
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- Bertrand Boisson PhD