Clinical Immunology of Immunodeficiencies: More than Just Recurrent Infections

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Thomas A. Fleisher, MD, FAAAAI, FACAAI
Executive Vice President, AAAAI
Scientist Emeritus, NIH Clinical Center

Disclosure

Conflict of Interest: nothing to disclose relevant to this presentation

Off label drug use: discussion based on publications describing non-FDA approved use of drugs in selected PIDs

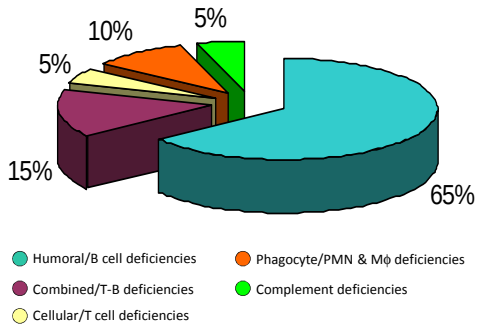
Lecture Objectives

- Diagnose CVID-like patients with monogenic genetic defects
- Recognize inflammatory complications in primary immunodeficiency patients with an eye to specific management approaches
- Develop a strategy for monitoring primary immunodeficiency patients for malignancy

PIDs and Susceptibility to Infections: Clues to the Immune Defect

	Bacterial	Viral	Parasitic	Fungal	Mycobact
T cells	X	X	X	X	X
B cells	X	X			
NK cells		X			
PMN cells	X			X	
MN cells	X				X
Complement	X				

Distribution of PIDs



Common Variable Immunodeficiency: A Tale of Two Clinical Phenotypes

Common Variable Immunodeficiency

- 1:30,000 Caucasians
- Patient is ≥2 years (some definitions ≥4 years)
- At least two isotypes are low for age: IgG plus IgA and/or IgM
- Poor antibody function documented (defective vaccine responses)
- Secondary causes have been excluded
  - Protein loss: GI disease, lymphatic loss, nephrosis
  - Infections: HIV, EBV, congenital rubella/CMV/Toxoplasma
  - Medications: steroids, rituximab, seizure medications,
  - Malignancy: thymoma, multiple myeloma, CLL
  - Other PID: congenital agammaglobulinemia, leaky SCID, X-linked lymphoproliferative syndrome, ataxia telangiectasia

Age at Presentation of Common Variable Immunodeficiency (CVID)

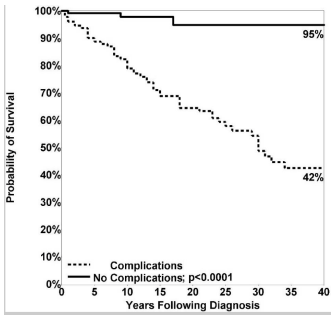
- Median age of symptom onset
  - Males = 23 years
  - Females = 28 years
- Median age at diagnosis
  - Males = 29 years
  - Females = 33 years
- This translates into a 5-6 year delay between onset of symptoms and establishing the diagnosis can have clinical consequences

Cunningham-Rundles Clin Imm 1999; 92:34

CVID: Two Clinical Phenotypes

- Infections without other complications (~1/3)
  - Normal life expectancy
  - Effective IgG replacement allows good quality of life
- Infections plus other complications (~2/3)
  - Autoimmunity: ~30%, particularly cytopenias
  - GI disease: ~15%
  - Granulomatous disease: ~10%
  - Lymphoma: ~8%
  - Splenomegaly: ~30-40%
  - Lympadenopathy: ~15%

Impact of Non-Infectious Complications on Survival in CVID



Resnick, et al. Blood 2012, 119:1650

Monitoring CVID Patients (Dr. Cunningham-Rundles)

Monitoring	Interval
Physical examination, history	12m
CBC, liver, kidney function, albumin	12m
IgG, A, M	6-12m (wt gain, pregnancy)
Pulmonary function	12m
Lung disease: High resolution CT scan	3-4 yrs or change in symptoms
GI disease: Endoscopy	According to symptoms
GI disease: Bone density	2y
GI disease: Nutritional evaluation	12m

Monitoring of CVID for Lymphoma

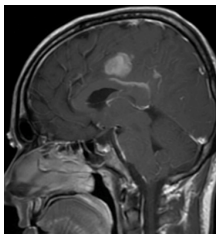
- 43 lymphomas reported in Mount Sinai series of ~650 CVID patients
- Include unusual presentations: small bowel, parotid, lung, mass on kidney
- Diagnosis established: chest CT, mammogram (axillary node invovlement), leg swelling (pelvic node), spine pain (retroperitoneal nodes)
- Take new complaints/changes reported by patients seriously - evaluate appropriately and follow closely

CVID and CVID-like Disorders with Defined Monogenetic Causes Often Are Associated with Findings of Immune Dysregulation

CVID-like Disease with Immune Dysregulation/Autoimmunity

CVID-like phenotype:
- Sinopulmonary infections
- Lymphadenopathy
- GI enteropathy
- Immune cytopenias
- Endocrinopathy
- Psoriasis, eczema, vitiligo
- Lymphoma

Genetic Testing:
Heterozygous (AD)
CTLA4 Mutations



Brain lesions involving grey matter and deep white matter: symptoms vary - include seizures, headaches, weakness

Kuehn, et al. Science 2014; 354:1623

Summary *CTLA4* Haploinsufficiency

- B cell dysfunction
  - Hypogammaglobulinemia
  - Recurrent sinopulmonary infections (IVIG/SCIG therapy)
- Autoimmunity
  - Lymphocytic infiltration of the brain, GI tract, lung
  - Autoimmune cytopenias
  - Endocrinopathy
  - Skin disease: eczema, vitiligo, psoriasis
- Immune dysregulation: Treg dysfunction, decreased CTLA4
- Treatment:
  - Rapamycin has been used successfully
  - Targeted therapy with a CTLA4 agonist (CTLA4-Ig/Abatacept) has been effective
  - ? Hematopoietic stem cell transplantation (HSCT)

CVID-like Disease: Immune Dysregulation/ Autoimmunity Due to LRBA Mutations

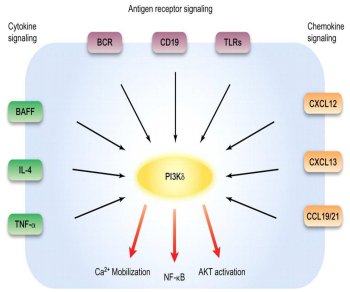
- Autosomal recessive defect increases CTLA4 turnover
- Recurrent sinopulmonary infections: ~60%
- Bronchiectasis: ~30%
- Hypogammaglobulinemia: ~40%
- Chronic diarrhea: ~60%
- Autoimmune disease: ~60%
- Growth retardation: ~40%
- Neurologic disease: ~25%
- T regulatory cell dysfunction
- Therapy: similar to *CTLA4* haploinsufficiency

Alkhairy et al. JACI 2016; 36:33

Another CVID-like Disease with Immune Dysregulation

- Recurrent sinopulmonary infections with decreased IgG and IgA, ± increased IgM levels
- Lymphadenopathy, splenomegaly
- Autoimmunity: cytopenias, enteropathy
- Mucosal lymphoid aggregates
- EBV (and/or CMV) viremia
- Increased risk of lymphoma
- AD gain of function mutation (GOF) affecting the p110δ phophatidylinositide-3-kinase subunit (PIK3CD)
- Similar clinical phenotype due to an AD mutation affecting PIK3R1, the p85α inhibitory protein

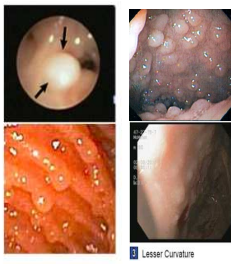
Heterozygous PIK3CD/PIK3R1 Mutations



Results in activated Phosphoinositide-3-Kinase δ Syndrome (APDS1/2)

Clinical and Lab Findings in APDS

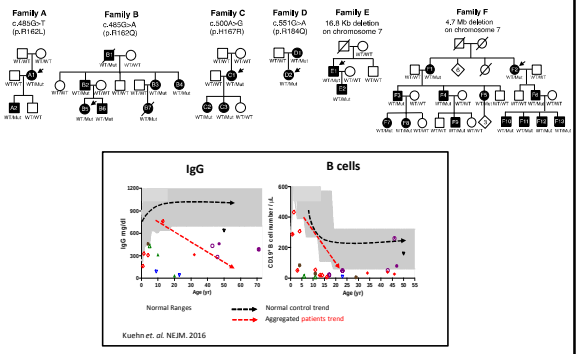
- Mucosal lymphoid hyperplasia (~33%)
- Neurodevelopmental delay (~20%)
- Increased IgM levels (~80%) but decreased specific antibodies
- Decreased CD4 T cells (>80%)
- Decreased naïve (CD45RA+/CD62L+) T cells and increased effector memory (CD45RA-/CD62L-) T cells
- Increased senescent ($CD57^{+}$) CD8 T cells & transitional ($CD38^{++}$) B cells
- Therapy
  - Rapamycin
  - Specific PIK3CD inhibitor (leniolisib) in phase 2 trial (Rao VK, et al Blood 2017)



Lung GI tract

Coulter, et al. JACI 2017; 139:597

Heterozygous Mutations in *IKAROS*

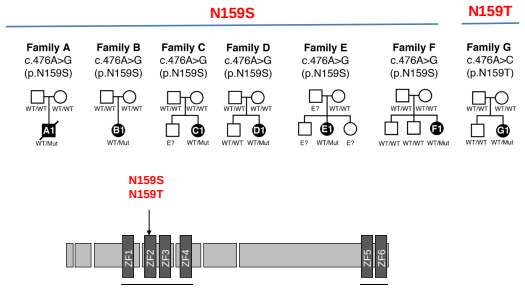


Kuehn, et al. NEJM 2016; 374:1032

Summary of IKAROS Haploinsufficiency

Total 45 germline IKAROS mutation carriers (14 families)	
Recurrent or severe bacterial infection	25 (56%)
Low B cells number	29 (64%)
Hypogammaglobinemia	34 (76%)
Childhood B-ALL	2 (4%)
Autoimmune disease (cytopenias, IgA vasculitis, systemic lupus erythematosus)	5 (11%)
Asymptomatic	12 (27%)

Mutations in *IKAROS* (N159S/N159T) in Patients with Combined Immune Deficiency



Boutboul D, et al
J Clin Invest, 2018

Phenotype of N159S/N159T *IKAROS* Mutations

Early presentation: 3 pts symptomatic <3 mo; all 7 pts <18mo	
Low B cells	7/7
Hypogammaglobinemia (IgG/A/M)	7/7
Low IgE	5/6
Neutropenia	5/7
Eosinopenia	6/6
PJP (*Pneumocystis* pnemonia)	7/7
Bacterial infection (*S. pneumo; Pseudomonas; Klebsiella)*	6/7
Viral infection (RSV, Adeno, Herpes)	5/7
Fungal (*Candida, Aspergillus*)	4/7
Cryptosporidia Sclerosing Cholangitis	1/7
T-ALL	1/7
Hematopoietic Stem Cell Transplant	3/7 (2 alive, 1 died)

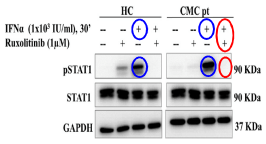
Summary of *IKAROS* Variant Patients

- Autosomal dominant disorder
- Varied immunodeficiency depending on the specific genetic defect (allelic variation)
- Variable penetrance with haploinsufficiency as some mutation + family members have little or no findings
- IKAROS deficiency can manifest as haploinsufficiency with a CVID-like presentation (increased infections, cytopenias, autoimmunity, malignancies) or as a dominant negative disorder presenting as a combined immune deficiency (PJP, viral/bacterial infections, cytopenias, low IgE/eos, T-ALL)

STAT1 Gain of Function (GOF/AD)

- Infections: chronic mucocutaneous candidiasis, sinopulmonary (bronchiectasis), mycobacteria, dimorphic molds (cocci, histo), HSV, VZV, RSV
- Autoimmunity (endocrine), GI problems (enteropathy, dysmotility, structural), arterial aneurysms, short stature, dental abnormalities
- Increased STAT1 phosphorylation:
  - Decreased Th17 cells (candidiasis)
  - Treg numbers and function are normal
  - Poor vaccine responses (>50% on IV/SCIG) and low memory B cells

Report of JAK Inhibitor Therapy in STAT1 GOF



IFNα induces increased STAT1 phosphorylation in patient cells
This can be blocked with a JAK inhibitor

Pre-rx 12 weeks post-rx

STAT1 GOF alopecia areata treated JAK inhibitor Ruxolitinib (JACI 2015; 135:552)

A recent review reported on 11 patients with STAT1 GOF treated with JAK inhibitors (Ruxolitinib, jakinhib) with the majority benefiting from jakinib therapy in terms of autoimmunity and immune dysregulation

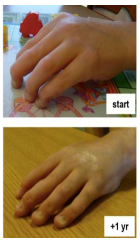
Forbes LR, JACI 2018, in press

STAT3 Gain of Function (GOF/AD)

- Symptoms start in childhood (mean ~5 yrs)
- Initial symptoms involve hematologic autoimmunity and lymphoproliferation
- Additional features of autoimmunity include: enteritis, diabetes, thyroid disease, arthritis, hepatitis, interstitial lung disease, skin disease
- Short stature may be found
- Lymphopenia and hypogammaglobulinemia
- Recurrent infections: ~60% usually respiratory, Herpes virus, candidiasis

Therapy of STAT3 GOF

Increased IL-6 in a patient with STAT3 GOF and arthritis raised the question if blocking IL-6 could be therapeutic



Blood 2015; 125:591-99

A recent review reported 6 patients with STAT3 GOF benefited from jakinib (with anti-IL6 blockade)

Forbes LR, JACI 2018, in press

CVID Summary

- CVID as a diagnosis of exclusion that has become more complicated with recent gene discovery
- ~25-30% of CVID-like patients are now found to have a monogenic cause (*e.g. CTLA4, PIK3CD*)
- Genetic evaluation of CVID/CVID-like patients is clinically indicated:
  - Family history of CVID/CVID-like disease (there are also *de novo* mutations particularly autosomal dominant forms)
  - Genetic diagnosis could result in an alternative approach to therapy beyond immunoglobulin replacement
  - Probably not clinically useful in settings where the genetic finding is associated with susceptibility rather than a cause (e.g., *TACI*)

Primary Immune Deficiency 2018

- It is now clear many of these diseases represent immune deficiency plus immune dysregulation
- Recurrent infections are often accompanied by evidence of autoimmunity (Alain Fischer found autoimmunity present in 26% of ~2200 PID pts)
- Phenotypic heterogeneity is a common feature
- Non-infectious complications appear to result from altered lymphoid development, active signaling, defects in central and/or peripheral tolerance, defective immune complex clearance and possibly other immunoregulatory abnormalities

"…the greatest teachers of modern immunology: patients with immunodeficiency diseases."

Robert A. Good, M.D., D.Sc., Ph.D.

Thank you