UT Southwestern Medical Center

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Title: Common Variable Immunodeficiency, much more common and complex

This is to acknowledge that Maite de la Morena, M.D. has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. de la Morena will not be discussing off-label uses in her presentation

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Academic Interests: My interest in Immunology started with the AIDS epidemic and quickly moved to the primary immunodeficiency diseases. I have been trained both in basic and clinical immunology. As a clinician I have expertise in the care of patients with congenital and acquired defects of immune function including: primary immune deficiency diseases (PID), autoimmunity, transplantation (both solid organ and stem cells). I joined the Department of Pediatrics and the Division of Allergy and Immunology at University of Texas Southwestern Medical Center (UTSW)/ Children's Medical Center in Dallas in the fall of 2005 to establish a clinical program for primary immunodeficiency diseases. It has become a Jeffrey Modell Center for diagnosis and treatment of primary immune deficiency diseases. The program cares for >300 patients with an established PID diagnosis and serves as a major referral center for the North Texas, Oklahoma, and neighboring states. In addition, I am an active referral consultant for the Texas Department of State Health Services to evaluate children with abnormal newborn screening for Severe Combined Immune Deficiency (SCID). The PID program is integrated with the hematopoietic cell transplant program at Children's Medical Center and we are an active member of the Primary Immune Deficiency Treatment Consortium (PIDTC). Both clinical and translational research infrastructure is in place. In collaboration with Dr. Nicolai van Oers, we have profiled microRNA expression patterns in patients with PID which uncovered a unique pattern in patients with 22q11.2 deletion. Subsequent studies have identified the role of microRNA in T cell homeostasis and discovered a new non-coding RNA in thymic development. With Dr. Ward Wakeland novel genes involved in human PID are being pursued. I have also lead a clinical multicenter study to understand the long term natural history of patients with X-linked hyper IgM syndrome. The PIDs continue to provide unique opportunities to further our understanding of the biology of normal human immune function.

Purpose: To educate and promote awareness of the primary immune deficiency diseases and their presentation during adult life. In particular, discuss the many clinical manifestations of common variable immunodeficiency (CVID), the most common defect of adaptive immunity in humans.

Title: Common Variable Immunodeficiency (CVID): Much more common and complex

Objectives:

- Discuss immunodeficiencies in adult patients
- CVID: Discuss the definition, epidemiology, clinical manifestations, genetics and clinical outcomes of patients
- Describe the principles of management of patients with CVID

The role of the immune system in human disease:

The immune system has evolved to allow individuals to live in a world of infectious microbes. The discovery of antimicrobials in the middle of the last century has allowed for the description of patients with defects of immune function. These patients became the experiments of nature that established the immune system as essential for host defense. To protect us from infectious microbes, the immune system utilizes a complex interactive network of cells, proteins, and organs. The primary lymphoid organs are the bone marrow, thymus, and spleen. The secondary lymphoid organs are the lymph nodes and lymphatics.

This complex system can distinguish between what belongs to the body ("self") from what is foreign to it ("nonself"). While this is effective in clearing infectious pathogens, this also applies to the rejection of tissues and organs. When the immune system becomes "dysregulated," an organism's "self" cells may become the target of attack leading to the development of autoimmune diseases. Other times, the immune system tends to react "in excess" against seemingly harmless substances such as pollens. This is the basis of hypersensitivity/allergies and asthma.

For the past 40 years it has also been known that the human immune system also contributes to cancer "control". The evidence for this includes examples of cancers arising when the immune system is weakened such as in patients with primary immunodeficiency disorders (PID), HIV, or transplant recipients receiving chronic immunosuppression. We also know that tumor specific antibodies and T-lymphocytes can kill tumor cells. Exploiting this knowledge has led to the development of targeted therapies for specific types of cancers.

Immunodeficiency syndromes may be classified as either primary or secondary**. Primary immunodeficiency** diseases are inherited disorders (usually caused by a single gene defect) and come to medical attention early in life. **Secondary immunodeficiencies** may be the consequences of infections (HIV is the classic example), autoimmunity, malignancies or the immunosuppressive effects of medications (Table1)

Differential Diagnosis of Hypogammaglobulinemia

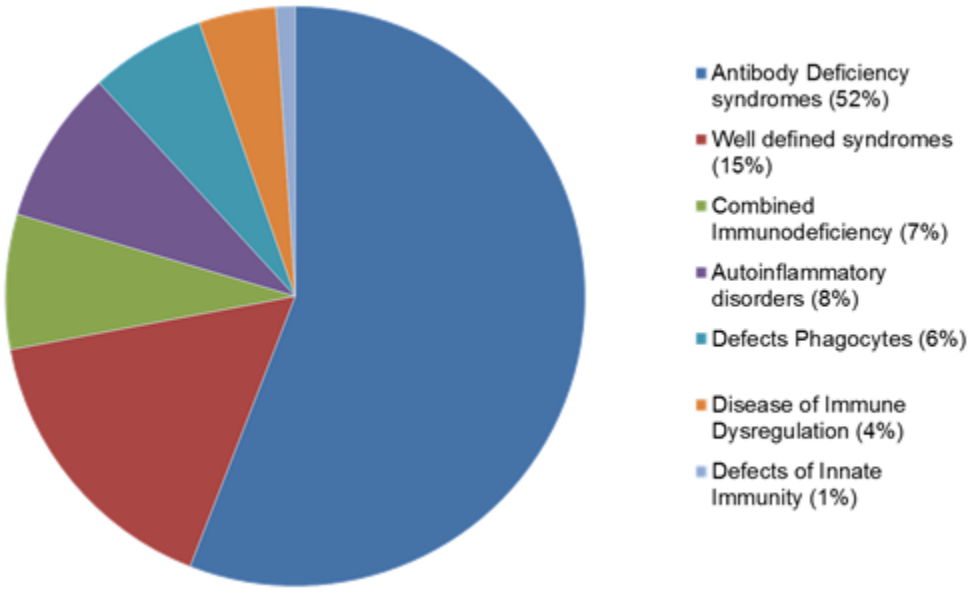
2 Drug	3 Malignancy	Infectious Diseases
Antimalarials agents	CLL	Human immunodeficiency virus
Antiepileptics	Thymoma + ID Good's Syndrome	Epstein-Barr Virus
Captopril	Non-Hodgkin's Lymphoma	Congenital CMV
Glococorticoids	Multiple Myeloma	Congenital *Toxoplasma gondii*
Fenclofenac	Waldestrom's macroglobulinemia	Congenital Rubella
Gold salts		
Penicillamine		
Phenytoin		
Sulfasalazine		
Rituximab		

4 Ongoing Losses	5 Other PID: Single gene defects
Nephrotic syndrome	Hyper IgM syndrome (XHIGM/CD40L)
Lymphangiectasias	Autosomal Recessive SCID
Protein losing enteropathy	Transcobalamine II deficiency
Burns	X-linked agammaglobulinemia
	X-linked lymphoproliferative disease
	Ataxia Telangiectasia

Table 1

Primary immune deficiency diseases (PIDs) are a diverse group of genetic disorders in humans with varied clinical heterogeneity that result in altered immune function. More than 280 PIDs have been identified thus far and the vast majority of these are monogenic defects, inherited in either non-Mendelian or Mendelian fashion. The estimated overall prevalence of the primary immunodeficiency diseases is generally accepted to be close to 1:10,000. This suggests that there may be approximately 400 new cases of primary immunodeficiency in infants born in the US each year (4.0 million live births in the US each year). Early and prompt diagnosis is essential as curable and life-saving therapies are available. If a molecular diagnosis is established, prenatal diagnosis can be offered to parents and family members.

Most immunodeficiencies are due to antibody defects (>50%). The clinical presentation of each PID depends on the component of the immune system that is deficient. It is important to understand that taken together, most patients with PID develop a lot of routine infections that will be seen by a non-specialist. Unless the practitioner thinks of PID in the right clinical scenario, these conditions may go undiagnosed.



Courtesy Jeffrey Modell Foundation Survey Data 2012-2013 N= 77,193

Clinical presentation of patients with antibody defects

1) Recurrent bacterial sinopulmonary infections or sepsis, particularly with encapsulated organisms
2) Chronic lung changes (bronchiectasis, pulmonary nodules or granulomas)
3) Chronic or recurrent gastroenteritis (often *Giardia* or enterovirus)
4) Chronic enteroviral meningoencephalitis
5) Autoimmunity: Arthritis and cytopenias
6) Organisms:
    a. Encapsulated bacteria (S.pneumoniae/HIB)
    b. GNR (pseudomonas)
    c. Atypical: Ureaplasma sp
    d. Enteroviruses
    e. Protozoa (Giardia)

Antibody defects recognized in adults include the following:

Antibody Deficiency Syndromes in Adults

	XLA	IgA deficiency	CVID
Age at onset	Congenital (> 6 mo)	Any age	Any (> 4 years)
IgG	Absent/low	Normal	Low
IgA	Absent/low	Absent or low	Normal/low
IgM	Absent/low	Normal	Normal/Low
B Cells	Absent/ low	Yes	Yes /low
Molecular Defect	BTK	No	CD19, ICOS, TACI, BAFF,
IgG Therapy	Yes	No	Yes

Common Variable Immunodeficiency (CVID)

CVID represents a group of heterogeneous primary antibody failure syndromes characterized by the following:

1. Clinical manifestations (at least one): Recurrent infections, autoimmunity, and /or lymphoproliferation
2. Low IgG below 2 SD below the mean for age
3. IgA and/or IgM must be low
4. Impaired antibody production to either TD or TI antigens
5. All other causes of hypogammaglobulinemia must be excluded (see table above)
6. Genetic studies for monogenic forms of CVID are not required

Prevalence of CVID: Estimated to be 1:10,000 -1:100,0000

Pathogenesis: Impaired adaptive immunity due to defective antibody production with or without loss of T-cell function. The underlying pathophysiology is not well understood.

Clinical manifestations: In addition to those recognized in patients with antibody defects noted above, patients with CVID can develop chronic lung disease. Lymphoid interstitial pneumonitis, follicular bronchiolitis and granulomatous lymphocytic interstitial lung disease (GLILD) is present in up to 20% of patients with CVID. Chronic lung disease is a major cause of mortality. Lung biopsy should be considered. The granulomas are non-caseating and may resemble sarcoidosis. Differences between GLILD and sarcoidosis are noted in the table below:

GLILD vs Sarcoidosis

GLILD	Sarcoidosis
Fatigue	Fatigue
Cough	Dyspnea
Splenomegaly 30%	Splenomegaly 15%
Uveitis rare	Uveitis 65%
Hx of infections 100%	?
PFT: Restrictive PFTs rare	PFT: Restrictive changes ~80%
Hypogammaglobulinemia	Polyclonal increase in IgG and IgA
Larger nodules Associated ground glass opacities, mid to lower lung zone	Micronodular nodules, perilymphatic upper lung zones
Hilar & Mediastinal Adenopathy	
bronchiolocentric	Perilymphatic
follicular bronchiolitis and LIP	
Non-necrotizing granuloma	
Random distribution	Perilymphatic

J Clin Immunol. 33(1):30-9, 2013)
Arnold Clin Immunol 2009

Autoimmune manifestations in CVID are common and present in up to 30% of patients. By far, ITP is the most common of the autoimmune cytopenias followed by autoimmune hemolytic anemia. Not uncommonly Evans syndrome may be a presenting manifestation. Gastrointestinal manifestations of autoimmunity can be seen in 15% of patients. When present may be refractory to standard therapies. If liver disease is present, histologic features are characteristic of nodular regenerative hyperplasia.

Malignancy is noted with an increased frequency as compared to the general population occurring in up to 10% of patients with CVID. By far, lymphomas are the most common form of malignancy and patients should follow standard of care therapies with the recognition of the patient's immunocompromised state. Malignancy is the second most important cause of death for patients with CVID.

Laboratory Investigations:

- Serum immunoglobulin levels: IgG, IgA, IgM
- CBC with differential: absolute lymphocyte count, platelet count and size,
- Renal (UA) and liver function tests including albumin for loss
- Serum IgG antibodies to vaccines
- Lymphocyte subpopulations: T, B and NK cells; B cells subsets
- Specific diseases – e.g. infectious etiologies: fungal or mycobacterial antigens (if granuloma), fecal fat (if malabsorption), sweat test (to exclude cystic fibrosis)
- Base line PFTs and CT (since bronchiectasis, fibrotic or interstitial disease are common complications)
- **USE CAUTION IN THE INTERPRETATION OF SEROLOGIC TESTS IN PATIENTS WITH ANTIBODY DEFECTS OR ON IgG THERAPY**

- Genetic Studies are generally not indicated as a polygenic origin is hypothesized. Monogenic etiologies: (ICOS, CD19, CD20, CD21, CD81, CD27, TWEAK, NFKB2, CTLA4 and LRBA) represent <5% of patients.

Treatment: Patients with CVID should be followed and managed by an Immunologist, a specialist with experience in the diagnosis and care of patients with primary immunodeficiency diseases. Multidisciplinary care for those experiencing complications is common. Immunoglobulin replacement therapy is essential. Both Intravenous route and subcutaneous routes of delivery are available. IgG doses should be titrated with clinical benefit. Monitoring adverse events includes measurement of liver and renal function, amongst others. Antibiotics are used frequently and prophylaxis has also been recommended by expert panel, though evidence is not well established.

Patients with CVID should not be given live vaccines. Family contacts should not receive attenuated polio vaccine.
MMR and varicella may be given to household contacts of CVID patients.
Some CVID patients may benefit from Inactivated Flu vaccine and should be offered.

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