Antibody deficiencies – CVID

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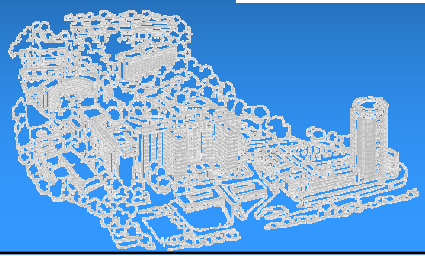
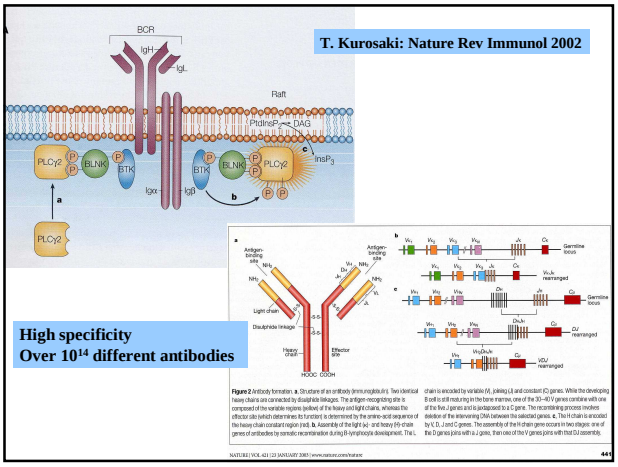
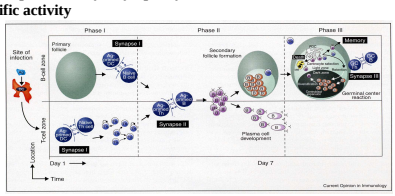




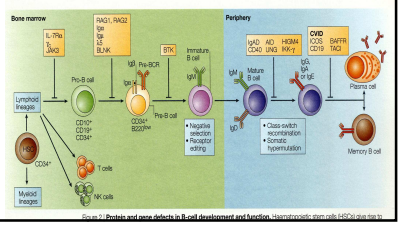
T. Kurosaki: Nature Rev Immunol 2002

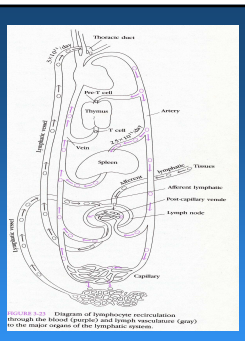
High specificity
Over 10^{14} different antibodies

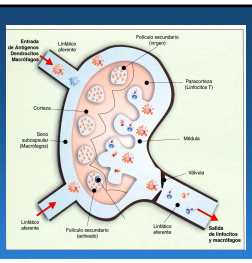
Igs are produced by B lymphocytes and need T-cell collaboration for a specific activity

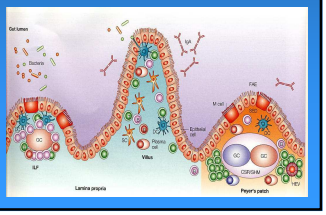


PID studies have improved understanding of the molecules involved in B-cell maturation









B cells are found in peripheral blood and tissues

Nat Rev Immunol

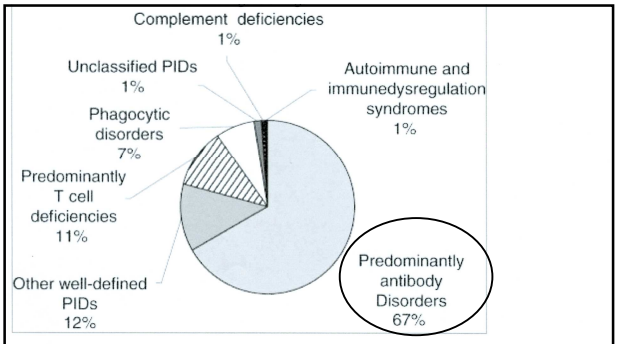
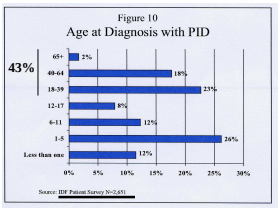


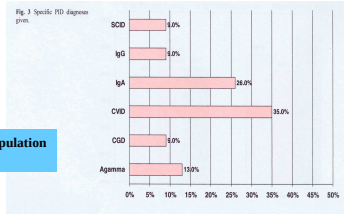
Fig. 2

Distribution of entries in the European Society for Immunodeficiencies (ESID) online database by main primary immunodeficiencies (PID) category.

Clin Exp Immunol. 2007 February; 147(2): 306–312.
doi: 10.1111/j.1365-2249.2006.03292.x.



The majority of PID diagnosed in adults are antibody deficiencies including IgA-D, and a proportion of patients, who are symptomatic, have CVID



Prevalence of PID: 1/ 1,200 general population
R. Buckley J Clin Immunol 2007

To date, the diagnosis of CVID has been made after ruling out other causes of hypogammaglobulinaemia (such as immunosuppressors, cystic fibrosis. protein losses...)

Definitions of CVI according to the ESID: (see also www.esid.org)

Common Variable Immunodeficiency (CVI)

Probable

Male or female patient who has a marked decrease (at least 2 SD below the mean for age) in two out of three of the major isotypes (IgM, IgG and IgA) and fulfills all of the following criteria:

1) Onset of immunodeficiency at greater than 2 years of age
2) Absent isohemagglutinins and/or poor response to vaccines
3) Defined causes of hypogammaglobulinemia have been excluded (see Table)

No molecular diagnosis is YET available

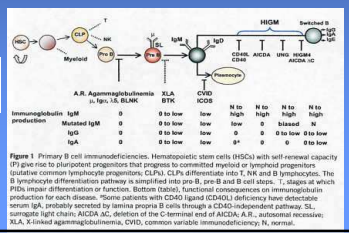


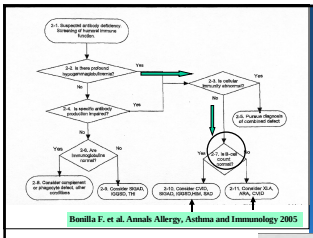
Figure 1 Primary B cell immunodeficiencies. Hematopoietic stem cells (HSCs) with self-renewal capacity (P) give rise to pluripotent progenitors that progress to committed myeloid or lymphoid progenitors (putative common lymphocyte progenitors; CLPs). CLPs differentiate into T, NK and B lymphocytes. The B lymphocyte differentiation pathway is simplified into pro-B, pre-B and B cell steps. T, stages at which PIDs impair differentiation or function. Bottom (table): functional consequences on immunoglobulin production for each disease. *Some patients with CD40 ligand (CD40L) deficiency have detectable serum IgA, probably secreted by lamina propria B cells through a CD40-independent pathway. SL, surrogate light chain; AICDA, AC, deletion of the C-terminal end of AICDA; A.R., autosomal recessive; XLA, X-linked agammaglobulinemia, CVID, common variable immunodeficiency; N, normal.

Diagnostic work-up of Antibody deficiency must begin with a thorough history of infections !!!

Diagnosis must include Ig subclass values, reponse to previous vaccines or present infections, and lymphocyte subsets.
New vaccines (*HiB and pneumococcus*) are used to demonstrate the poor or normal antibody response

On many occasions the diagnosis of infection VERSUS allergy (bronchitis..) is NOT clear-cut!
Of help: good general status and development
- **good recovery from infections**
- **family history, etc**

If under 3 years of age → could be a transient hypogammaglobulinaemia→careful follow-up



Bonilla F. et al. Annals Allergy, Asthma and Immunology 2005

Recognizing Primary Immune Deficiency in Clinical Practice H. Yarmohammadi et al. Clin Vaccine Immunol. 2006

TABLE 1. Scores of diagnoses and conditions assessed from the clinical record

Diagnosis or condition	Score	Diagnosis or condition	Score
Pneumonia, organism unknown	3	Malabsorption	2
Bacterial pneumonia	3	Giardiasis	2
Septicemia	3	Autoimmune hemolytic anemia	2
Empyema	3	Chronic sinusitis*	1
Bronchiectasis	3	Chronic bronchitis*	1
Osteomyelitis	3	Chronic otitis media	1
Other abscess	3	Chronic diarrhea*	1
Aseptic meningitis	3	Acute bronchitis	1
Splenic abscess	3	Acute sinusitis	1
Chronic mastoiditis*	3	Fever of unknown origin	1
Bacterial meningitis	3	Cutaneous candidiasis*	1
Liver abscess	3	Suppurative otitis media	1
Lung abscess	3	Failure to thrive	1
Lymphopenia	2	Thrush	1
Cellulitis	2	Lymphadenitis	1
Neutropenia	2	Gastroenteritis	1
Splenomegaly	2	Mycosis	1
Lymphadenopathy	2	Acute otitis media	1
Immune thrombocytopenia	2	Abnormal weight loss	1

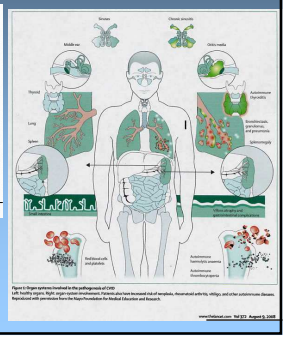
* Diagnoses counted as chronic conditions counted only once in a 12-month period.

If antibodies are the neutralising agents of infections, mainly those of extracellular dissemination, it is clear that hypogamma will be characterised by repeated and/or not responding bacterial infections

Table 1 Typical infections in primary antibody deficiency

Microbe	Clinical presentation
Pneumococci	pneumonia/septicemia/meningitis*
Haemophilus influenzae type B	pharyngitis/septicemia/meningitis*
Meningococci	meningitis/septicemia*
H. influenzae (non-typeable)	bronchitis/sinusitis/otitis media†
Streptococci	bronchitis/sinusitis/otitis media†
Moraxella catarrhalis	bronchitis†
Mycoplasmas	arthritis/urethritis/otitis media**
Enteroviruses	meningoencephalitis/myositis**
Campylobacter pylori	enteritis**
Giardia lamblia	enteritis**

Maintaining trough IgG level at ~7 g/l: *prevents systemic spread of infection; **provides partial protection; †provides poor protection – many patients require prophylactic antibiotics



Some IgA deficiencies can "become" CVID

Immunological Data

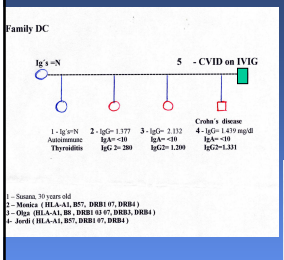
	Case 1st	Case 2nd	Case 3rd
	Diagnosis of IgA-D/CVID	Diagnosis of IgA-D/CVID	Diagnosis of IgA-D/CVID
Age (years)	8/14	7/8	14/26
IgG (g/liter)	6.96 3.16	7.58 2.16	9.84 4.40
IgM (g/liter)	1.26 0.87	1.8 0.2	0.86 0.25
IgA (g/liter)	0.01 und.	und. und.	und. und.
IgG1 (g/liter)	5.20 3.20	4.81 2.04	n.d. 3.60
IgG2 (g/liter)	0.54 0.02	0.85 0.05	n.d. 0.02
IgG3 (g/liter)	0.18 0.01	0.71 0.3	n.d. 0.30
CD3 (%)	71 74	49 88	n.d. 68
CD4 (%)	n.d. 54	17 18	n.d. 46
CD8 (%)	n.d. 37	31 69	n.d. 26
B cells (%)	22 18	12 4	n.d. 15
ANA (titer)	1/50 neg.	1/2560 1/20	n.d. neg
Anti-DNA (U/ml)	7.4 neg.	74.2 neg	
HLA	A 24, 11 B38,39-DB3,4	A9, 26 B51,18-DR1,4	n.d.

Note. und., undetectable; n.d., not done; neg., negative.
* Control values (median) of IgG subclasses at different ages from Plebani (16) and our controls.

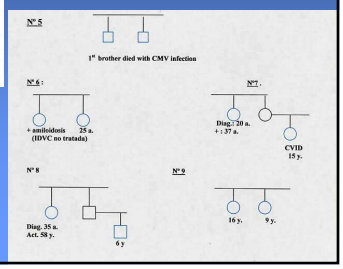
2nd case- The girl was diagnosed of SLE and corticoids were started. Owing to her history of previous infections, an immunological work-up and strict follow-up were made. A CVID was diagnosed 1 year later. Since IVIG therapy was started, she has been completely asymptomatic.

T.Espanol et al 1999

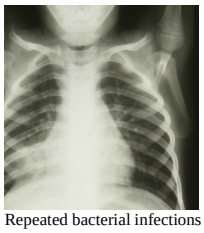
Family incidence of IgA-D and CVID



CVID in families



Some cases are EASILY diagnosed

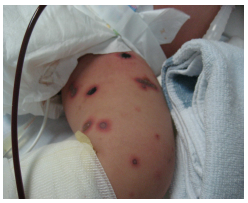


Repeated bacterial infections
Low IgG, M and/or A
B cells present in peripheral blood

With/without family history

↓

CVID



Severe bacterial infections
All Igs low
Male and no B cells

With/without family history

↓

XLA

"Difficult" diagnosis

A 12-year-old girl was diagnosed of CVID. She had several episodes of AIHA and ITP, treated with corticoids. On admission, she had considerable respiratory distress. Lung biopsy -->lymphocytic infiltration of CD3+ cells.

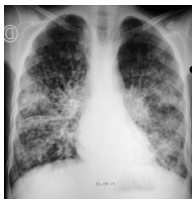
IgG : 519 mg/dl

CD19 = 16%

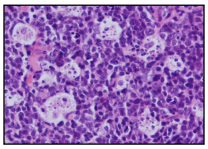
She began with IVIG; however, that therapy was irregular and after a diarrhoea episode IgG:155 mg/dl

She is currently on IVIG and immunosuppression

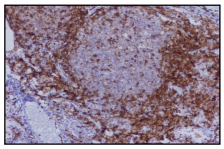
Family history:A maternal aunt had a similar clinical history. Diagnosed of CVID at 25 years of age, she died at the age of 27 when on the lung transplant waiting list.

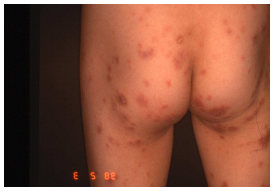


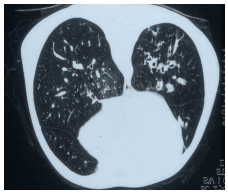
HE 400X



Anti-CD3 100X







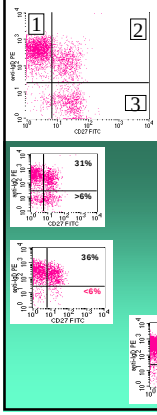
A 6-year-old girl was diagnosed of hypogammaglobulinaemia (IgG=210, M=20 A=0 mg/dl) and treated irregularly with IVIG. Repeated bacterial infections and also Candida and Campylobacter.

She was also treated with corticoids for an AIHA. Lymphopenia was observed.

Skin biopsy: Granuloma annular. Lympho-histiocytic infiltration. Negative cultures

She died from respiratory infections at the age of 17.

Analysis of B-memory cells helps to classify different forms of CVID with different prognoses



1: CD27- IgD+: naïve B-cells;
2: CD27+IgD+: memory non-switched B cells;
3: CD27+IgD-: mature B-memory cells.

	MB0 (naïve)	MB1 (memory)	MB2 (mature)	
Recurrent respiratory tract infection at diagnosis	18 (100%)	13 (81%)	6 (86%)	NS
Recurrent diarrhea at diagnosis	11 (61%)	6 (37%)	3 (43%)	NS
Bronchiectasis	16 (89%)	11 (69%)	0 (0%)	NS
Chronic lung disease	9 (50%)	2 (13%)	0 (0%)	<0.05
Malabsorption	9* (50%)	3 (19%)	0(0%)	<0.05
Splenomegaly	11 (61%)	4 (25%)	1 (14%)	<0.05
Lymphadenopathy	11 (61%)	4 (25%)	0 (0%)	<0.05
Autoimmune cytopenias	4 (22%)	3 (19%)	0 (0%)	NS

D.Detkova et al CHEST 2007

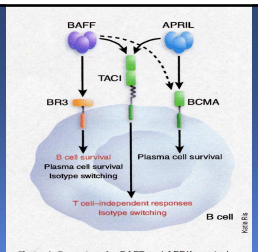


Figure 1 Receptors for BAFF and APRIL control B cell development and function. Red indicates rate-limiting functions.

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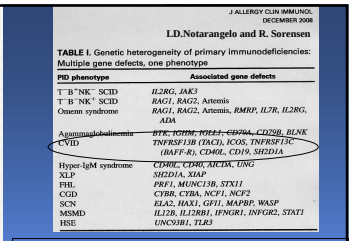

J ALLERGY CLIN IMMUNOL
DECEMBER 2008

LD.Notarangelo and R. Sorensen

TABLE I. Genetic heterogeneity of primary immunodeficiencies: Multiple gene defects, one phenotype

PID phenotype	Associated gene defects
T⁻B⁻NK⁻ SCID	*IL2RG, JAK3*
T⁻B⁻NK⁺ SCID	*RAG1, RAG2,* Artemis
Omenn syndrome	*RAG1, RAG2,* Artemis, *RMRP, IL7R, IL2RG, ADA*
Agammaglobulinemia	*BTK, IGHM, IGLL1, CD79A, CD79B, BLNK*
CVID	*TNFRSF13B (TACI), ICOS, TNFRSF13C (BAFF-R), CD40L, CD19, SHD1A*
Hyper-IgM syndrome	*CD40L, CD40, AICDA, UNG*
XLP	*SH2D1A, XIAP*
FHL	*PRF1, MUNC13B, STX11*
CGD	*CYBB, CYBA, NCF1, NCF2*
SCN	*ELA2, HAX1, GFI1, MAPBP, WASP*
MSMD	*IL12B, IL12RB1, IFNGR1, INFGR2, STAT1*
HSE	*UNC93B1, TLR3*

Barcelona and P. de Mallorca groups

BLOOD, 24 SEPTEMBER 2009 - VOLUME 114, NUMBER 13

Table 2. Frequencies, significance for monoallelic and biallelic *TNFRSF13B* variants in patients and control group: presence of variants in healthy first-degree relatives (HFDR)

Genotype	CVID	Controls	P	HFDR
p.C104R/p.C104R	6/120	0/198	.006	3
p.C104R/wt	2/120	5/198	n.s.	21
p.C104R/A181E	1/120	0/198	n.s.	1
p.L171P/p.L171R	1/120	0/198	n.s.	n.a.
p.L171R/wt	1/120	0/198	n.s.	n.a.
p.E140K/wt	1/120	0/198	n.s.	n.a.
p.C89Y/wt	1/120	0/198	n.s.	n.a.
p.E117G/wt	1/120	0/198	n.s.	n.a.
p.A181E/wt	0/120	0/198	n.s.	3

χ^2 test compared CVID and control group.
n.s. indicates not significant; and n.a., not available.

Around 10% of CVID cases have a demonstrated specific defect (TACI, CD19…) However, there is no clear relationship with clinical severity

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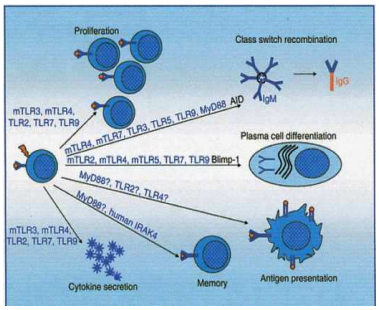
The role of different innate immunity molecules in the pathogenesis of CVID is a recent field of research



Immunology 2009; 128:311

Main problems during follow-up of CVID:

- Bronchiectasis
- Gastrointestinal manifestations:
  - Nodular hyperplasia
  - T-cell infiltrates, granulomas..
  - Malabsorption...
- Some viral infections (e.g.CMV)
- Lymphoproliferative diseases
- Autoimmune diseases

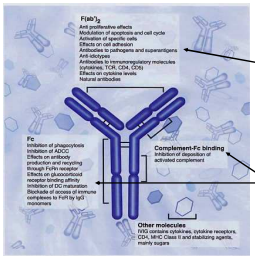
Cunningham-R C. Blood Rev 2002

Table I **Congenital immunodeficiency disease and autoimmune syndromes**

Autoimmune syndrome	Immunodeficiency disease
IgA deficiency and common variable immunodeficiency	• ITP • Autoimmune hemolytic anemia (AHA) • Rheumatoid arthritis • Pernicious anemia • Juvenile rheumatoid arthritis
Hyper IgM syndrome	• Neutropenia • ITP • AHA
Inherited defects of complement	• SLE • Vasculitis • Glomerulonephritis • Henoch–Schonlein purpura
Autoimmune lymphoproliferative disease	• ITP • AHA • Neutropenia
Mucocutaneous candidiasis	• Diabetes • Hypoadrenalism • AHA
Wiskott–Aldrich syndrome	• Juvenile rheumatoid arthritis • AHA

Antigens are neutralised by antibodies produced during infections.
Ig molecules (G,M,A,D and E).They have **different functions** and are very **specific** for each antigen or allergen. These molecules are found in plasma and in tissues.

Functions of IgG molecules



Jolles S et al. Clin Exp Immunol 2005

HOW to suspect and diagnose primary antibody deficiencies:

1st - **consider them** (and know how they present)
2nd – take a good clinical and family history
3rd - interpret laboratory results correctly
(**simple tests can be very informative)**

And remember : Not all PID have the same severity, and they are more frequent than many doctors think !!
Early therapy is the only way to avoid sequelae and permit good quality of life