Rheumatic manifestations of immunodeficiencies

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PID-AUTOIMMUNITY

- **PID PHENOTYPES: INFECTION /AUTOIMMUNITY**
- **PID HELP TO STUDY AND UNDERSTAND IMMUNE SYSTEM MECHANISM ASSOCIATED WITH AUTOIMMUNITY**
- Why would an immune system that is incapable of effective responses to foreign antigens seemingly be capable of responding to host antigens and causing autoimmunity?

JAPAN N=2900 PIDs / AID=8,5%

Endocrine disorders	Diabetes mellitus		Hypothyroidism	
	T1D	T2D	Hashimoto's thyroiditis	Non-autoimmune
Estimated prevalence in PID patients	93	16	47	109
Prevalence in the general Japanese population	1.19	0.461[†]	ND	13.5[‡]

Ped Internat 2013; p 671

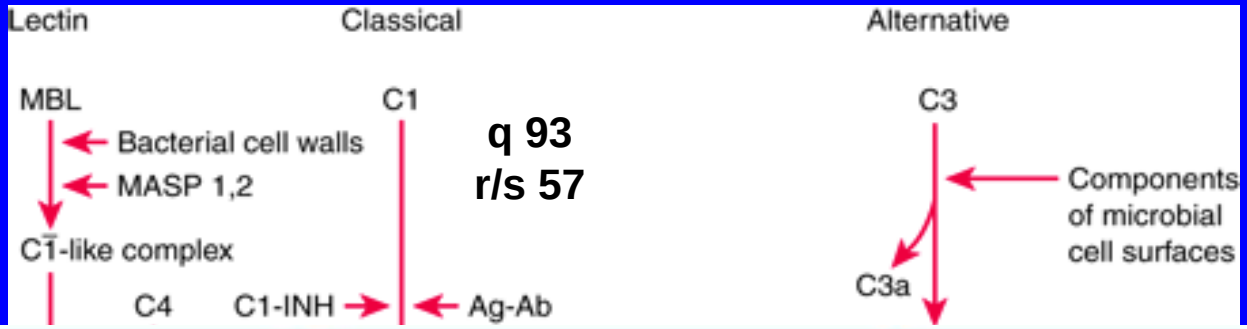
BRAZIL N=72 JSLE / AID=22%

6/16 COMPLEMENT DEFECTS

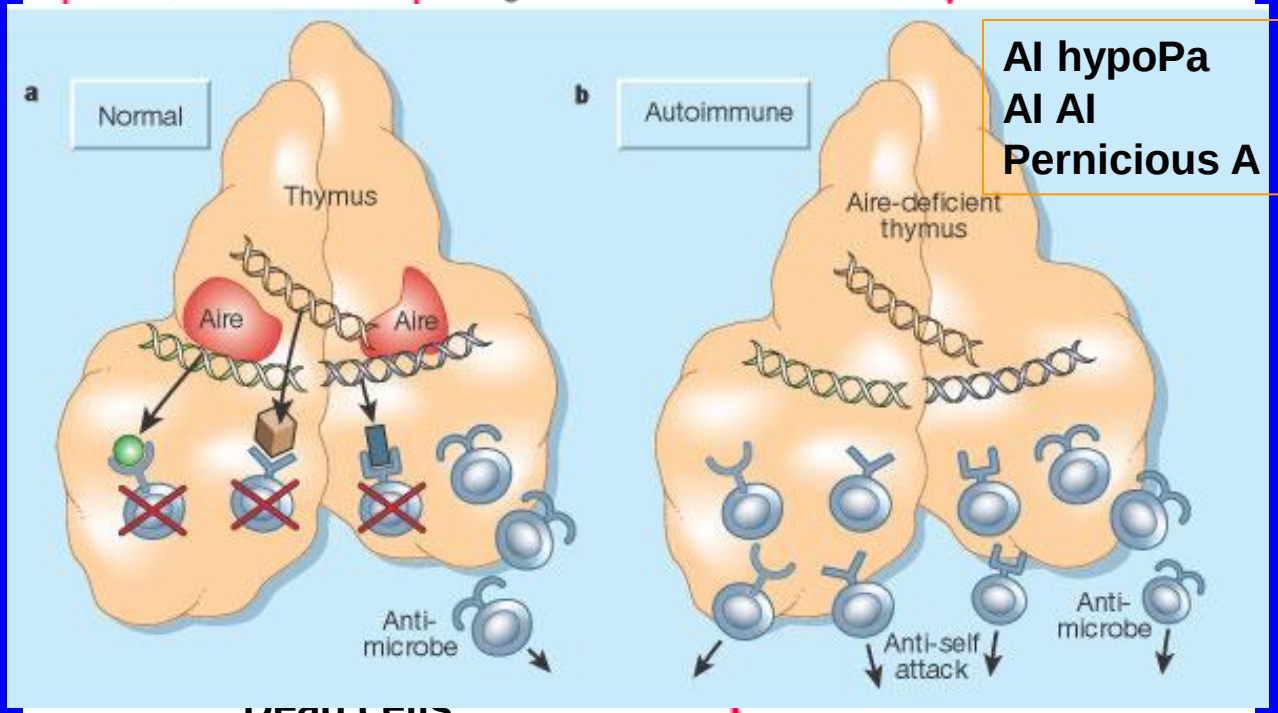
10/16 IMMUNOGLOBULIN DEFECTS

SIgAD 3 / IgG2D 4 / IgM 3

Lupus 2011; p1275

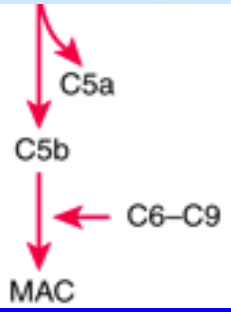


q 93
r/s 57



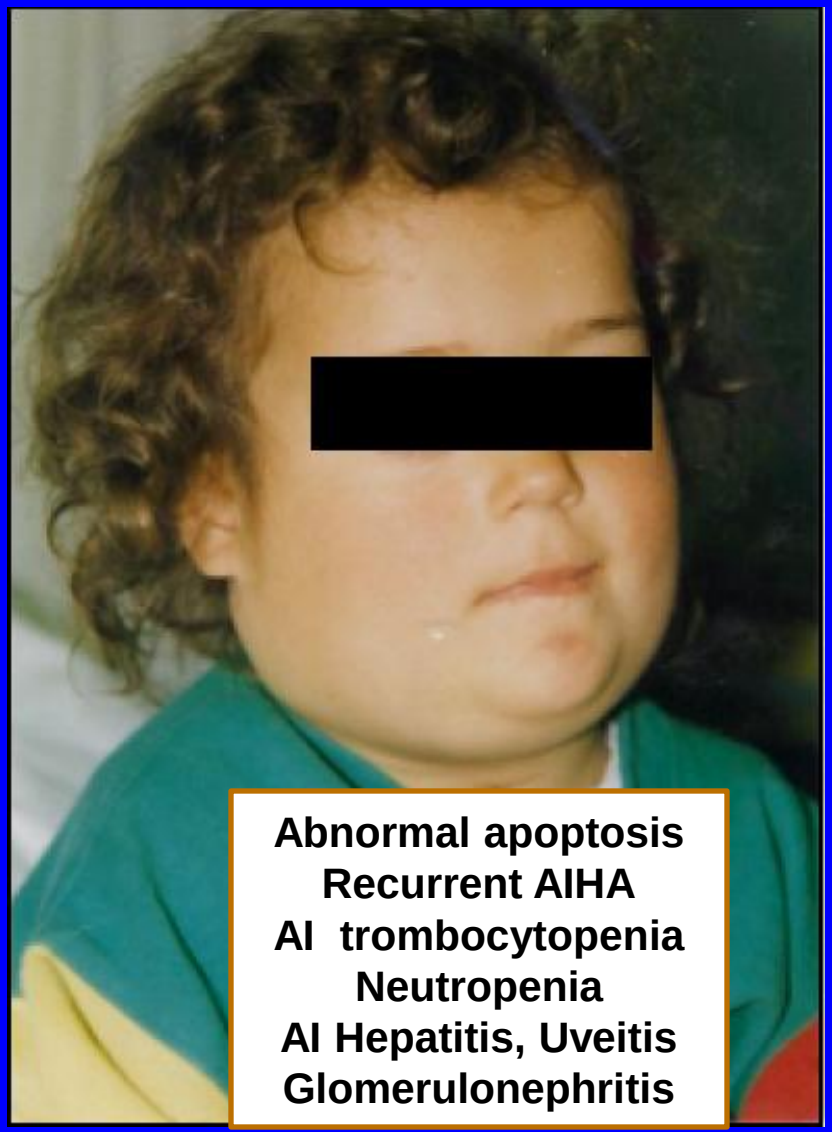
AI hypoPa
AI AI
Pernicious A

Dead cells
Generation of inflammation and autoantibodies

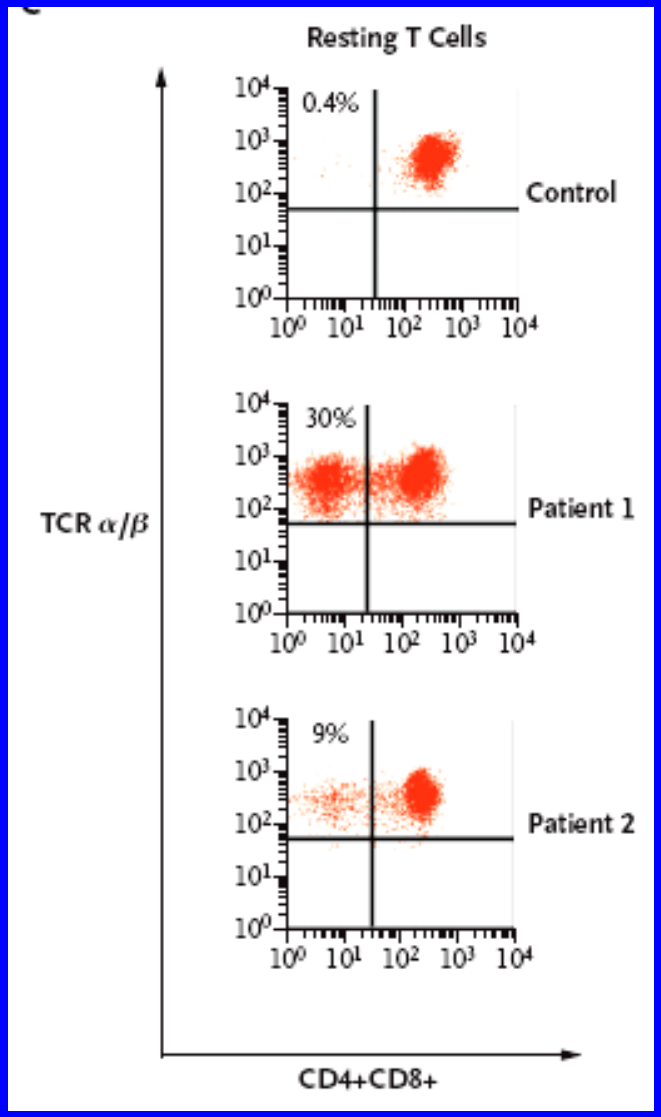


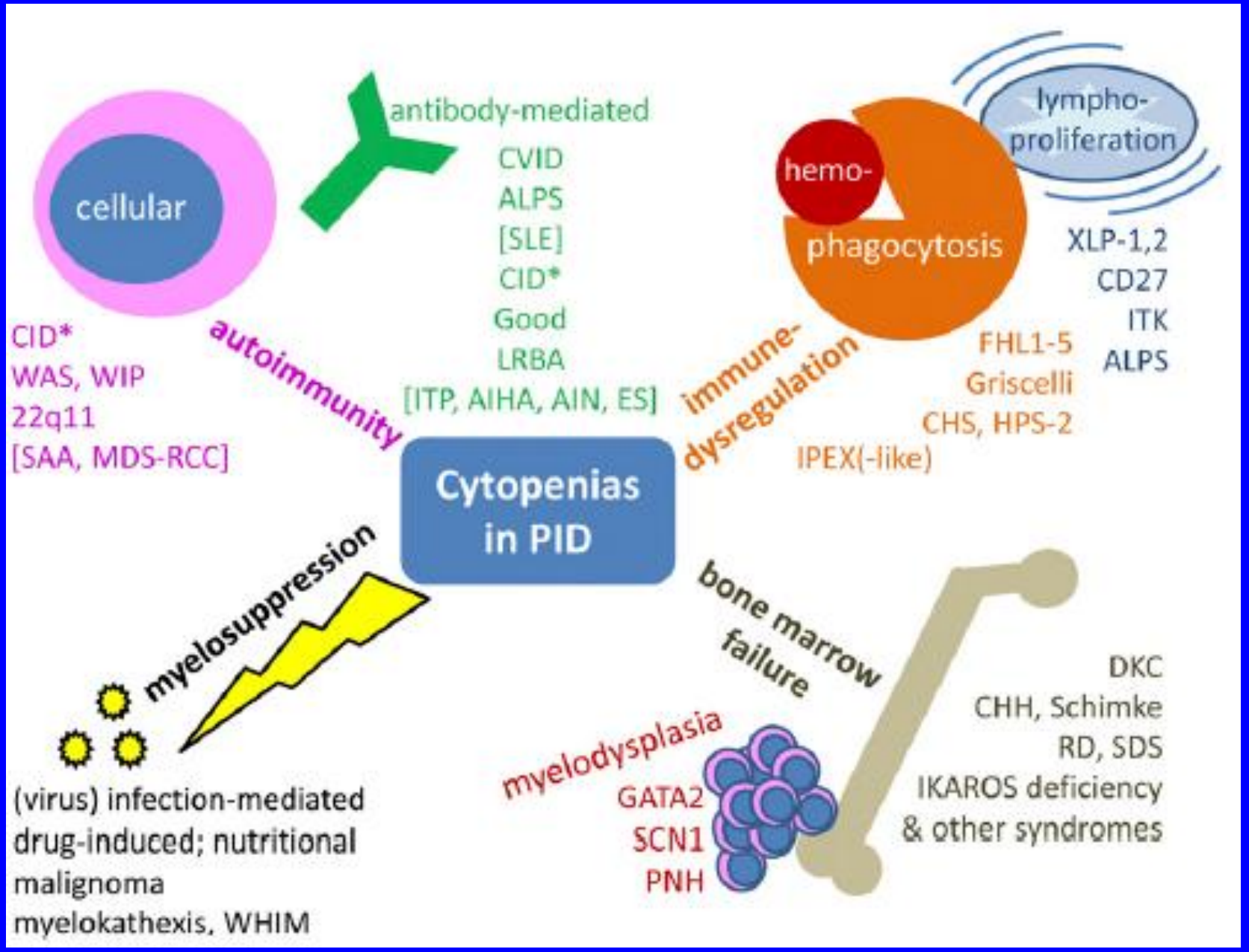
Autoimmune Lymphoproliferative Syndrome with Somatic *Fas* Mutations

HOLZELOVA E. NEJM 2004; 351:1409



Abnormal apoptosis
Recurrent AIHA
AI trombocytopenia
Neutropenia
AI Hepatitis, Uveitis
Glomerulonephritis





Blood 2014; p 2337

Primary immunodeficiency / Autoimmune disease			T-cell			Complement									B-cell					Complex[b]		
			IPEX	APECED	Omenn syndrome	C1q def.	C1r/s def.	C4 def.	C2 def.	C3 def.	MBL def.	C4A*Q0 due to AH8.1	C4A*Q0 - exon 29 mutation	C4B*Q0	ALPS	X-linked CD40L def.	AID def.	CVID	IgAD	WAS	NEMO def.	XLA
Systemic	ICD	SLE				93	57	75	32–33	10	sp.	sp.	sp.					1–3	0–1			
		Vasculitis		2–3					sp.	sp.					sp.			1–2		20–29		
		Henoch-Scönlein Purpura						8						sp.								
	Other	Sjögren's/Sicca syndrome		12				4										1–10	0–1			
		Arthritis/RA/JRA									sp.				4	11	3	1–4	3–5	20–29	3	15–20
		Psoriasis																	3–4			
		Sarcoidosis																sp.	2–4			
Organ-specific	Blood	Autoimmune haemolytic anaemia	30	2											29–39	2–3	3	2–3	2–3	15–36	1	sp.
		Autoimmune thrombocytopenia	14												23–34	sp.	3	3–8	0.5	d		
		Autoimmune neutropenia	sp.												18–19	>60[c]		1		25		sp.
	Endocrine	Type 1 DM	73	2–20													3	sp.	sp.			sp.
		Autoimmune thyroid disease	16–28	2–11												2		1–3	3–7			
		Autoimmune hypoparathyroid disease		76–93																		
		Addison's disease		70–100															sp.			
	Other	Glomerulonephritis					9	4	sp.	sp.					3–14				1	4		sp.
		Autoimmune hepatitis		20											sp.	6–20	7	1	1			
		Inflammatory bowel disease														2		6–10	0–1	9	21	sp.
		Coeliac disease																0–1	1–4			
		Autoimmune enteropathy	97%	10													3					
		Pernicious anaemia		13–15														1–9	1–2			
		Alopecia		32–37														2–4				sp.
		Vitiligo		8–15														0–13	1–4			
		Other autoimmune skin disease	62		100																	
		Guillain–Barre syndrome													1–3							
Total		Autoimmune prevalence (%)	100	~100	100	93	60–66	90	32–33	>10	Rare	Rare	Rare	Rare	>80	20	21–25	20–26	7–36	30–72	23–25	11–20
Ref.			11,12, 14,15	11,12,16, 17	12	18	18,20	18,20	18,20	18,20	25	30–32	79	34	12,51, 53	37,40	39	74,81, 82	63,64, 67,74	12.43	47	80

Scand J Immunol 2010; p 317

	%
Systematically associated	**>80**
IPEX (immunedysregulation polyendocrinopathy enteropathy X-linked syndrome)	100[b]
Omenn syndrome (OS)	100
APECED (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy)	Almost 100
ALPS (autoimmune lymphoproliferative syndrome)	More than 80
C1q deficiency	93

J Clin Immunol 2008, 28:s1:4-10

IDP-AUTOINMUNIDAD

- ***FOXP3*: T regulatory cells**
- ***AIRE-1:* thymic lymphocyte selection and tolerance**
- ***RAG 1, RAG 2, ARTEMIS:***
  somatic rearrangement, TCR and BCR repertoire restriction
- ***FAS: apoptosis***
- **C1q: immune complex and apoptosis debris clearence**

Strongly associated	**<80, >20**
C4, C1r/C1s, and C2 deficiencies	75, 65, and 10–25
Selective IgA deficiency	7–38
CVID (common variable immunodeficiency)	26
Hyper-IgM type 2 (AID deficiency)	21–25
XL-Hyper-IgM (CD40L deficiency)	20
Wiskott–Aldrich syndrome	40–72
NEMO deficiencies (XL-EDA-ID)	23

Mildly associated	**<20**
C3 and C5–9 deficiencies	
XL-agammaglobulinemia	11–15
Incomplete Di George syndrome	5–10
Chronic granulomatous disease	
Neutropenias	
Hyper-IgE syndrome	
MHC Class I deficiency	
MHC Class II deficiency	
FcγRIIIb deficiency	

<10%

Asplenia
Factor D deficiency
IL-12/IL-23–IFN-γ axis deficiencies
Ataxia telangiectasia syndrome
IRAK-4 deficiency
WHIM syndrome

PID-AUTOIMMUNITY

- Search for PID, if the AID:
  - Susceptibiliy to infections
  - Early onset
  - Is associated with allergy
  - Allergy and infections
  - > 1 organ specific AID
  - Family history of PID
  - ARTHRITIS + ABNORMAL GROWTH
  - ARTHRITIS + NEUTROPENIA

PID-AUTOIMMUNITY

- WISKOTT-ALDRICH SYNDROME
- AID ARE 3-10x > FREQUENT THAN IN NORMAL PEOPLE

IDP-AUTOINMUNIDAD

- **IL12/IL23-IFNγ // IFN γ R1 R2 STAT1**
- **NOT ASSOCIATED TO AID**

PID-AUTOIMMUNITY

- IPEX
- IMMUNEDYSREGULATION, POLYENDROCRINOPATHY, ENTEROPATHY, X-LINKED SYNDROME
- DM ID, TIROIDITIS, AI HEPATITIS, AIHA/ITP
- Ig NORMAL, CD3+ CD4+ CD8+ CD19 NORMAL

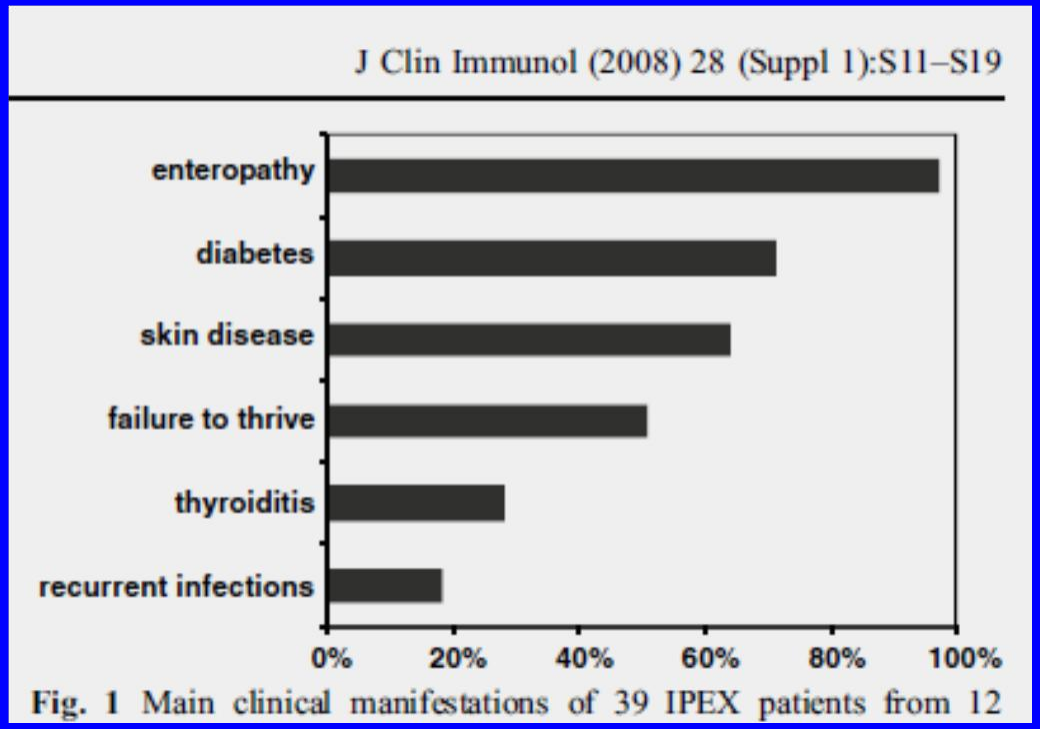


Fig. 1 Main clinical manifestations of 39 IPEX patients from 12

AIRE and immunological tolerance: insights from the study of autoimmune polyendocrinopathy candidiasis and ectodermal dystrophy

Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED): a model disease to study molecular aspects of endocrine autoimmunity

CLINICA	%
HPT	79
ADDISON	72
OVARIC DYSF	60
DM	12
HyPT	4

CANDIDA	100
D UÑAS	52
KERATOPATHY	35
VITILIGO	13
ANEMIA P	13
AI HEPATITIS	12
H ESMALTE	77

Selective IgA deficiency

40 AID- vs 17 AID+

Progression to CVID
Years of follow up
Higher IgM level
Higher Leucocyte count
Higher %Treg
% Class switching def.

J Investig Allergol Clin Immunol 2015; p112

Patient	Sex	Age at Diagnosis, y	Autoimmune Disorders	IgA, mg/dL
1	Female	4	DM + thyroiditis	0
2	Female	5	Celiac disease	0
3	Female	4	AIHA	0
4	Male	11	Vitiligo + thyroiditis	6
5	Female	11	Alopecia universal	7
6	Female	5	AIHA + thyroiditis	0
7	Male	9	Celiac disease	0
8	Male	4	Vitiligo + myasthenia gravis	5
9	Female	26	Crohn disease	5
10	Male	10	JRA	0
11	Male	9.5	Ulcerative colitis	5
12	Female	4	Vitiligo	7
13	Male	7	AIHA + DM + JRA	6
14	Male	9.5	Alopecia areata	4
15	Male	9	Type 1 diabetes	7
16	Male	10	Type 1 diabetes	7
17	Female	4	ALPS	0

PID-AUTOIMMUNITY

PID	AUTOIMMUNE MANIFESTATIONS
CHRONIC GRANULOMATOUS D	INFLAMMATORY BOWEL D
COMMON VARIABLE ID	ITP, H ANEMIA, RA, IBD, SLE, NEU
IgA DEFICIENCY	HYPOTHYROIDISM, SLE, CYTOPENIAS
OMENN SYNDROME	ENTEROPATHY, ALOPECIA
IPEX	DM-1, IBD, HYPOTHYROIDISM, CYTOPENIAS

PID-AUTOIMMUNITY

- **PID MOST BE INCLUDED IN THE DIFFERENTIAL DIAGNOSIS OF AID**
- **IMMUNE SYSTEM MECHANISM THAT EXPLAIN AID FISIOPATHOLOGY**