6th AME National Meeting
3rd Joint Meeting with AACE
VERONA 27-29 Ottobre 2006

CLASSIFICATION OF POLYGLANDULAR AUTOIMMUNE SYNDROMES

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AZIENDA OSPEDALIERA UNIVERSITA' PADOVA

STUDIUM GENERALE PADUANUM

Criteria for defining a disease as autoimmune

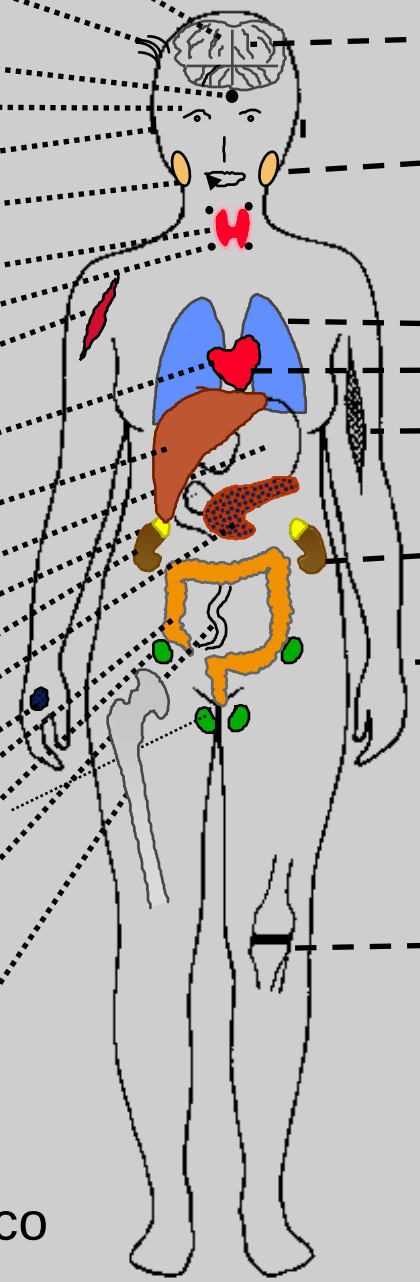
- Major criteria
- Presence of circulating autoantibodies or cellular immune-mediated events.
- Presence of lympho-plasmocytic infiltration in the target tissues.
- Induction of the disease in animals by means of injection of autoantigens and passive transfer of the disease by serum or lymphocytes.

- Minor criteria
- Association with other autoimmune diseases.
- Correlation with the MHC genes.
- Responce to immunosuppressive therapy.

(Witebsky and Rose 1957)

Malattie autoimmuni organo-specifiche

- Sistema nervoso
- Apparato pilifero
- Ipofisi
- Occhio
- Cartilagine
- Gh. salivari
- Tiroide
- Paratiroidi
- Muscoli
- Cuore
- Fegato
- Stomaco
- Surreni
- Reni
- Pancreas
- Cute
- Colon
- Gonadi
- Intestino
- Sistema emopoietico



- Sistema nervoso
- Ghiandole salivari
- Polmoni
- Cuore
- Muscoli
- Reni
- Cute
- Articolazioni

LES
AR
Sclerod

Malattie autoimmuni non-organo-specifiche

Definition of the Autoimmune Polyglandular Syndrome (APS)

…..as the coexistence of multiple autoimmune glandular failure or best (of multiple autoimmune diseases) in a patient.

Neufeld and Blizzard 1980

CLASSIFICATION OF APS

APS-1 (APECED) **Whitaker's syndrome**	**Chronic candidiasis** **Hypoparathyroidism,** **Addison's disease** ***(at least***
APS-2 **(Schimdt's syndrome or** **Carpenter's syndrome)**	**Addison's disease** ***(always present)*** **+** **thyroid autoimmune diseases and/or Type 1** **diabetes mellitus**
APS-3 **(Thyro-gastric syndrome)**	**Thyroid autoimmune diseases** **+** **other autoimmune diseases** ***(escluding: Addison's)***
APS-4	**Combinations not included in the previous groups**

Neufeld and Blizzard 1980

APS-1 o APECED
(Autoimmune polyendocrine-candidiasis ectodermal dystrophy)

Chronic candidiasis Addison's disease
Chronic Hypoparathyroidism
(at least two)

+
other autoimmune and non-autoimmune diseases

+
ectodermal dystrophy

EurAPS: Autoimmune polyendocrine syndrome type I: a rare disorder of childhood as a model of autoimmunity

contract number 2005-005223

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PREVALENCE OF APS-1

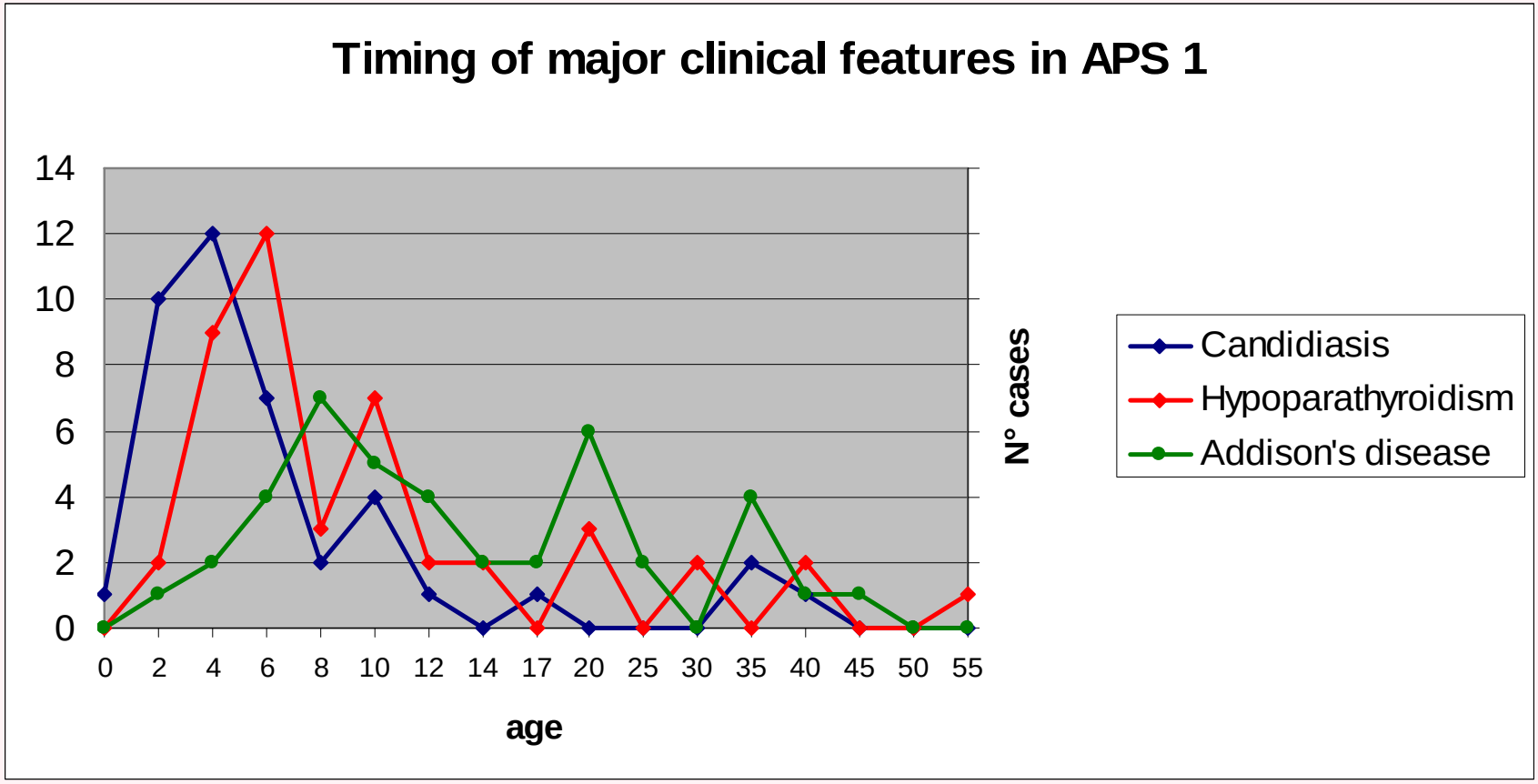
110 cases / million	Jewis (Iran)
60 cases / million	Sardinia
40 cases / million	Finland
15 cases / million	Puglia
12 cases / million	Norway
8 cases / million	Ireland
4 cases / million	Italy
0.1 cases / million	Japan

SPA di tipo 1: frequenza delle patologie nelle diverse popolazioni

	IRAN	SARDEGNA	USA	FINLANDIA	SUD ITALIA	NORVEGIA	GIAPPONE	SLOVENIA	NORD ITALIA	Irlanda	TOT
N° Pz	(23)	(18)	(20)	(78)	(11)	(20)	(7)	(12)	(55)	(31)	(279)
PATOLOGIE (%)											
CANDIDIASI	17	83	80	100	100	85	86	100	84	80	17-100
IPOPARATIROIDISMO	96	88	100	85	100	85	71	83	89	84	71-100
M. ADDISON	22	83	95	72	82	80	43	58	82	68	22-95
IPOGONADISMO	38	28.	15	39	18	20	n.d.	8	21,8	30	8-39
GASTRITE /A. P.	9	33	n.d	15	27	0	n.d.	n.d.	23,6	10	9-33
ALOPECIA	13	33	40	27	n.d	40	14	33	34,5	19	13-40
TIREOPATIE	4	0	25	6	36	10	n.d.	25	18,2	7	0-36
EPATITE	n.d.	22	25	13	27	5	n.d.	8	21,8	10	5-27
VITILIGO	n.d.	17	10	13	n.d	25	n.d.	8	21,8	n.d.	8-25
MALASSORBIMENTO	n.d.	28	5	10	18	10	14	25	9,1	n.d.	5-18
DM DI TIPO 1	4	5.5	n.d	18	0	0	43	8	7,3	10	0-43
CHERATOPATIA	0	17	n.d	22	n.d	10	n.d.	16,7	9,1	7	0-22
DISTROFIA ECT.	n.d.	n.d.	n.d	52	n.d	10	n.d.	41,7	n.d.	n.d.	10-52
DECEDUTI	n.d.	n.d.	n.d	13,2	n.d	n.d	n.d	n.d	14,5	10	13-14,5
F/M	1,1	n.d.	1.5	1	0.8	0.8	0.75	0.33	1.75		0.8-1,75

AGE AT ONSET OF THE MAIN DISEASES IN 55 ITALIAN PATIENTS

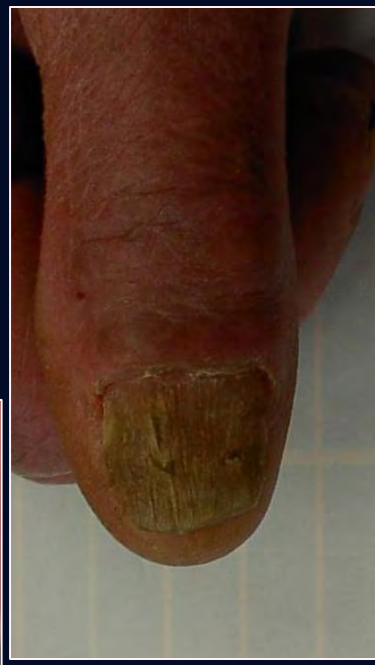
2nd EurAPS Meeting

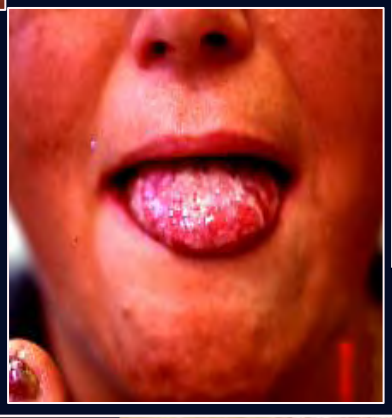
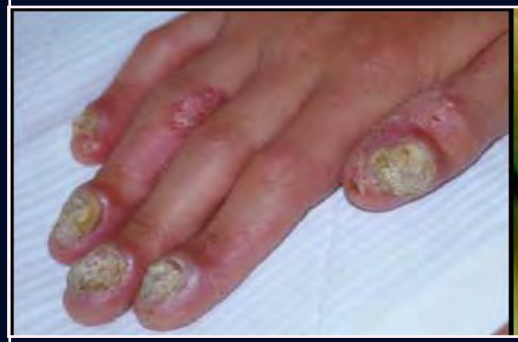
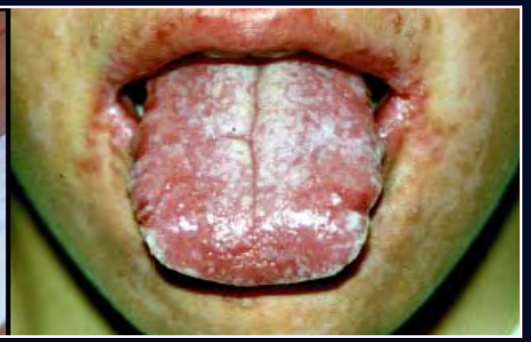


Chronic mucocutaneous candidiasis (CMC)

- CMC affects the nails, the dermis, the oral, vaginal, oesofageal mucous membranes
- It is limited to not more than 5% of the body surface
- CMC is the expression of a T-lymphocyte defect with inhability to react agaist candida antigens, but the numbers of peripheral lymphocytes are in the normal range
- The B-lymphocyte response to candidal antigens is normal and prevents the development of systemic candidiasis
- Periodical treatment with itraconazole can induce remission





Chronic Hypoparathyroidism (CH)

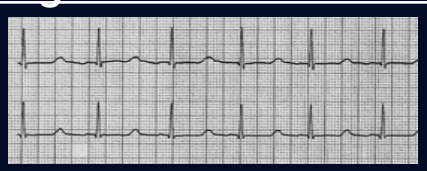
General features

- CH is the first endocrine disease to occur
- In neonatal period it is important to distinguish CH from genetic forms:
  - -Di George's syndrome
  - -Kenney-Caffey's syndrome
  - -Barakat's syndrome

Segno di Trousseau (tetania latente)

Manifestazioni cliniche

- **tetania**
- **convulsioni**
- **disturbi psichiatrici**
- **scompenso cardiaco reversibile**
- **cataratta sottocapsulare**
- **QT prolungato**



Q-T prolungato, alterazioni ST

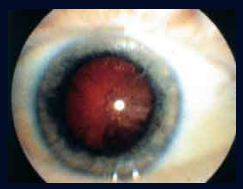
Pathology

- Parathyroid tissue from patients with CH is atrophic with a lymphocytic infiltration but frequently the parathyroid tissue is not detectable

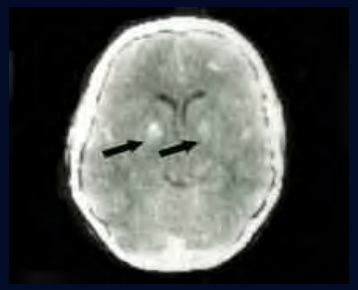
SUMMARY AUTOPSIES 11 CASES IDIOPATHIC HYPOPARATHYROIDISM PLUS ADDISON'S DISEASE

	Cases Abnormal	Cases Normal
Parathyroid glands	11	
No tissue found	9	
Fatty replacement	1	
Atrophy & atypical cells	1	
Adrenal cortex	11	0
Pronounced atrophy	11	
Lymphocytic infiltration	8	
Loss of lipid	3	
Fibrosis	3	
Adenoma	1	
Adrenal medulla	7	1
Atrophy	4	
Lymphocytic infiltration	4	
Thyroid gland	4	4
Decreased colloid	2	
Chronic inflammation	4	
Pituitary gland	4	2
Decrease in basophilic granules	4	
Pancreas	4	
Chronic inflammation	3	
Cystic fibrosis	1	
Pseudocyst	1	

McIntyre Gass, Am J Ophtalmol 54:660;1962

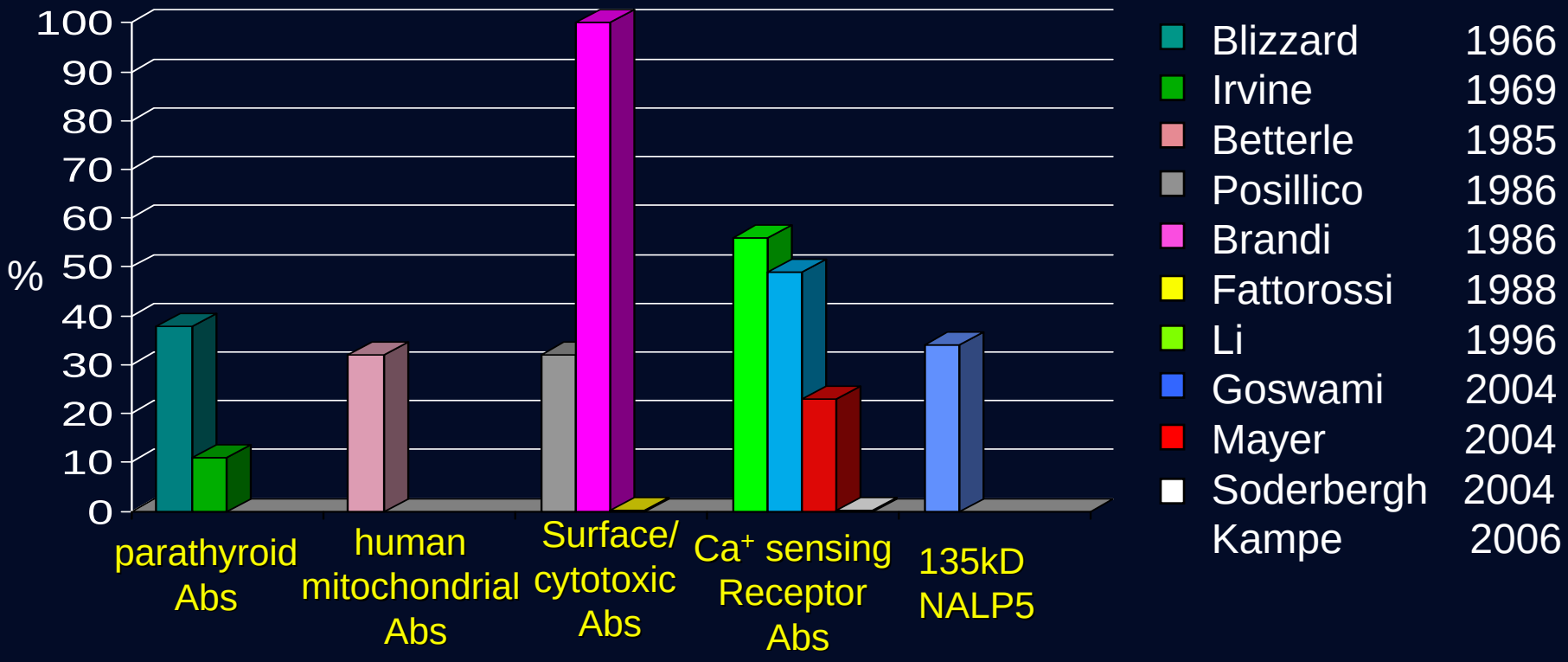


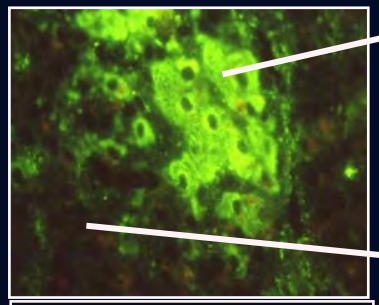
Calcificazioni sublenticolari



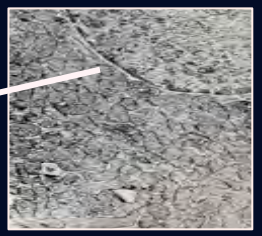
Calcificazioni sublenticolari

APS TYPE 1: PARATHYROID AUTOANTIBODIES

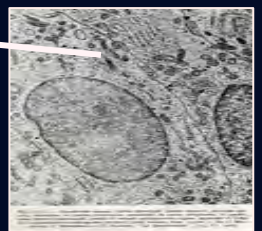




Paratiroid Abs



Oxyphil Cells (rich in mitochondria)

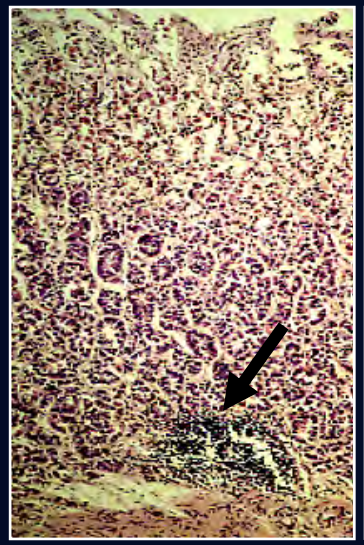


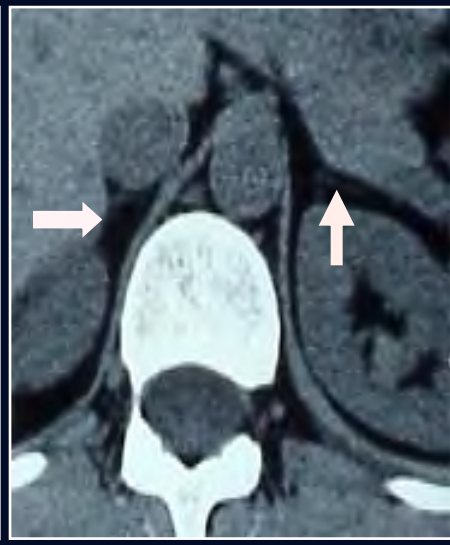
Chief Cells

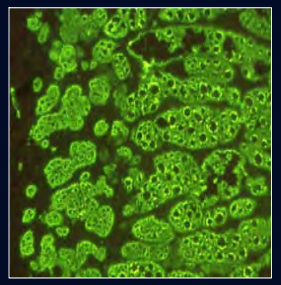
Addison's disease is the second endocrine disease to appear

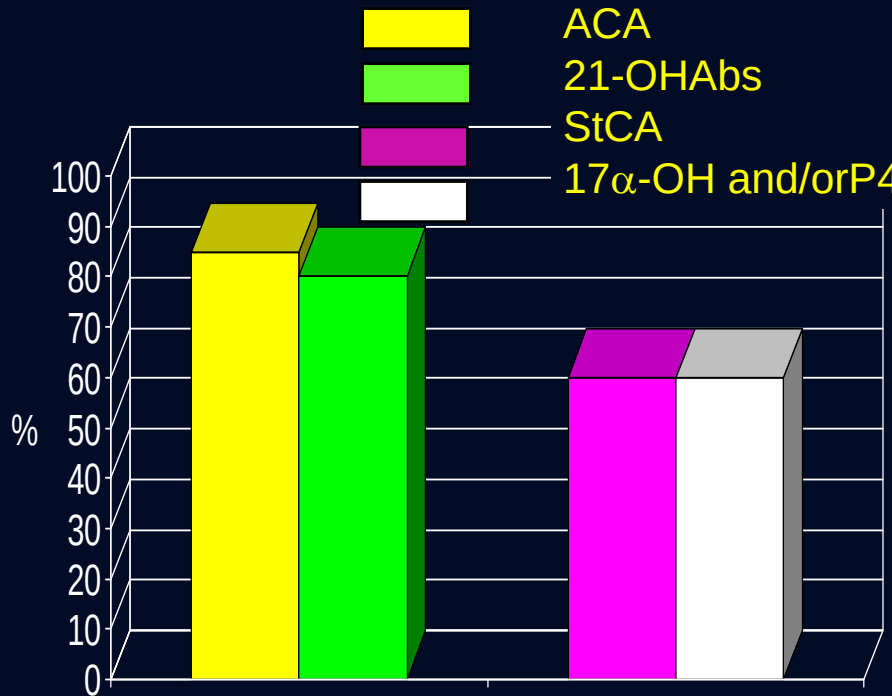
Pathology and imaging

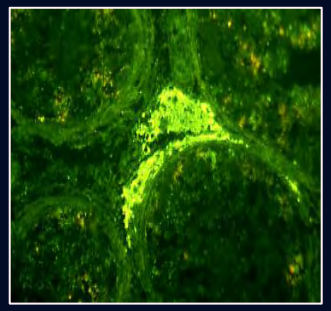
The adrenal glands from patients with AD is atrophic with lymphocytic infiltration but sometimes the adrenal tissue is not detectable







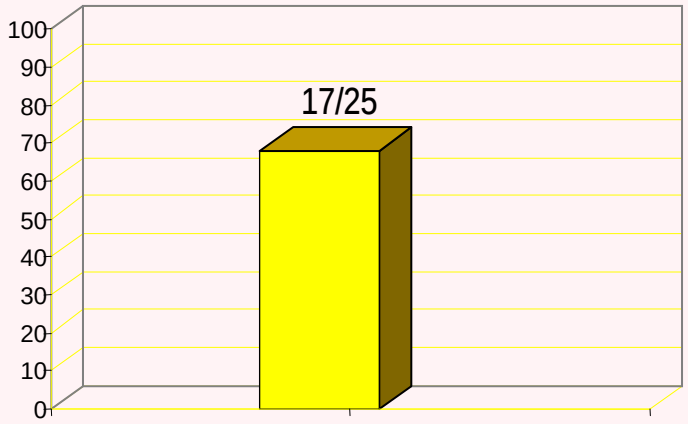




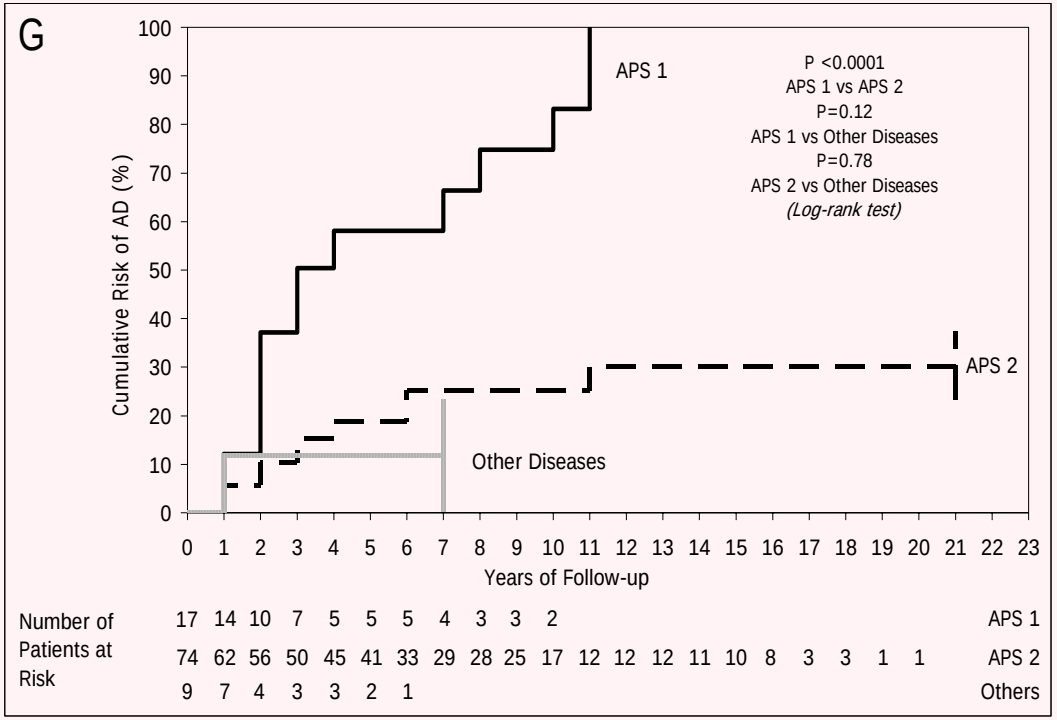
Can we predict **Addison's disease** in patients with one **component of APS-1?**

25 patients were tested

% ACA+



Cumulative risk for ADDISON in 17 ACA/21OHAb+ patients



Coco et al. JCEM 2006

SPA di tipo 1: frequenza delle patologie nelle diverse popolazioni

Provenienza	IRAN	SARDEGNA	USA	FINLANDIA	SUD ITALIA	NORVEGIA	GIAPPONE	SLOVENIA	NORD ITALIA	Irlanda	TOT
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MALASSORBIMENTO	n.d.	28	5	10	18	10	14	25	9,1	n.d.	5-18
DM DI TIPO 1	4	5.5	n.d	18	0	0	43	8	7,3	10	0-43
CHERATOPATIA	0	17	n.d	22	n.d	10	n.d.	16,7	9,1	7	0-22
DISTROFIA ECT.	n.d.	n.d.	n.d	52	n.d	10	n.d.	41,7	n.d.	n.d.	10-52
DECEDUTI	n.d.	n.d.	n.d	13,2	n.d	n.d	n.d	n.d	14,5	10	13-14,5
F/M	1,1	n.d.	1.5	1	0.8	0.8	0.75	0.33	1.75		0.8-1,75

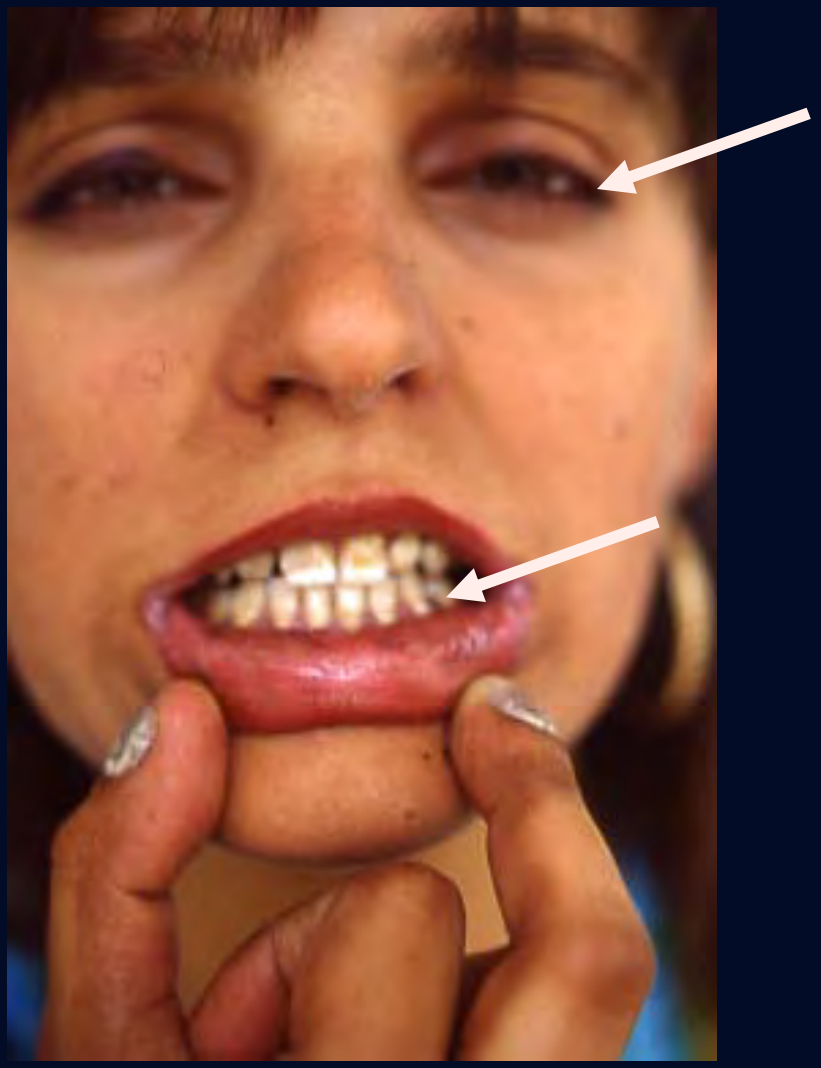
FREQUENCY AND AGE AT ONSET OF THE DISEASES IN 55 ITALIAN PATIENTS WITH APECED

F/M Children/Adults Family history	1.8/1 17/1 11 cases	mean age at onset (years)
Chronic Candidiasis	83.0%	6.9
Chronic Hypoparathyroidism	90.0	10.6
Addison's disease	83.0	14.8
Type 1 DM	7.4 %	5.7
Malabsorption	7.4	6.6
Keratoconjunctivitis	9.3	8.7
Hypophysitis	3.7	9.5
Alopecia	35.2	10.7
Vitiligo	20.4	14.8
Atrophic gastritis with/without PA	20.4	15.7
Chronic hepatitis	24.0	16.2
Sjögren's Syndrome	11.1	20.3
Hypergonadotropic hypogonadism	24.2	22.5
Thyroid autoimmune diseases	16.7	30.4
Cancer	7.4	44.0

SPA-1: AUTOANTICORPI NELLE MALATTIE MINORI

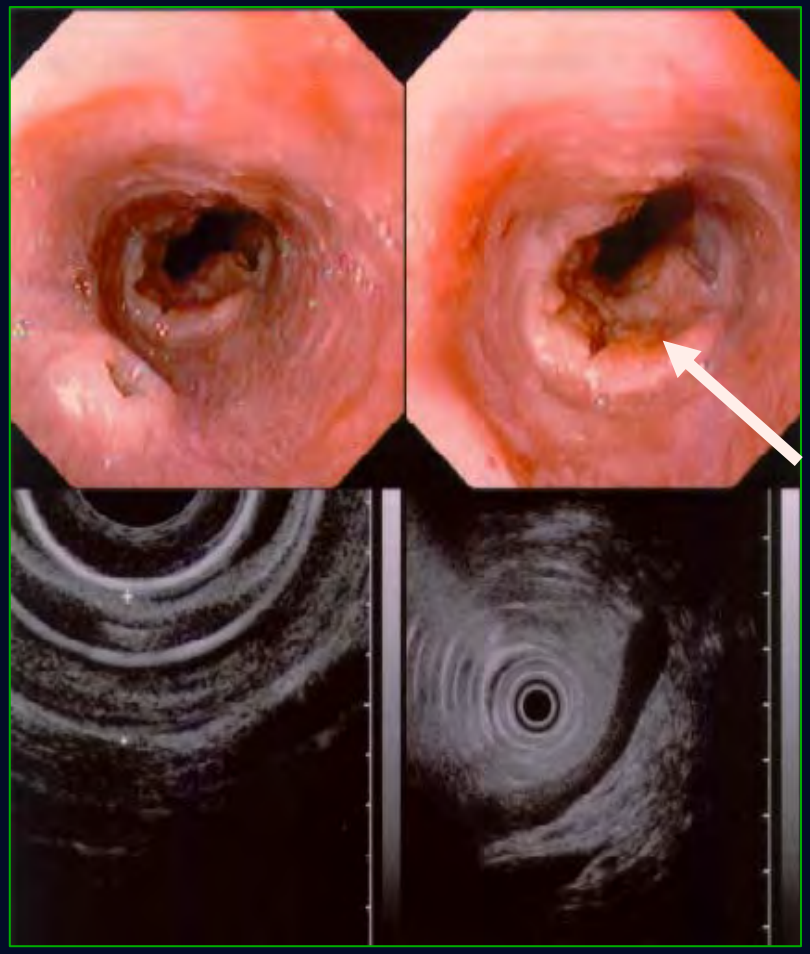
At the onset of	Autoantibodies	Before the disease
Hypergonadotropic hypogonadism	Steroid-producing cells (StCA), 17alfa-OHAb, P450sccAb	yes
Vitiligo	complement-fixing melanocytes Abs, anti-fattori di trascrizione SOX9 e SOX10	yes ?
Autoimmune hepatitis	anti-microsomi di fegato e rene (LKMA) anti-P450-IA2, anti-P450-2A6	yes ?
Celiac disease	Endomysium Abs Transglutaminase Abs (?)	yes ?
Type 1 diabetes	islet-cell antibodies (ICA) GADAbs, IA2Abs	yes yes
Thyroid autoimmune diseases	Thyroperoxydase Abs Thyroglobulin Abs	yes yes
Autoimmune gastritis Pernicious anemia	Parietal cells Abs (PCA) PCA + Intrinsic factor Abs	yes yes
Malabsorption	tryptophan hydroxylase Abs histidine decarboxylase Abs	? ?
Alopecia areata	tirosine hydroxylase	?

APS -1: ectodermal-dystrophy

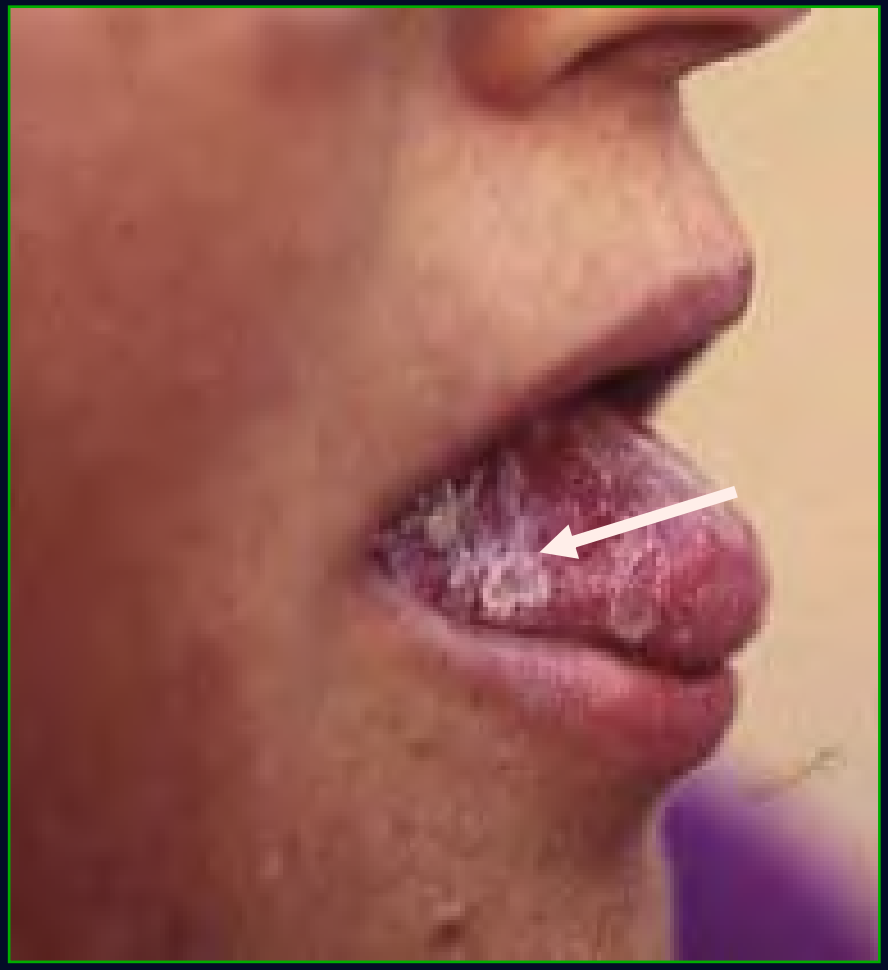


APS Type 1 and Cancer

Cancer of oesophagus

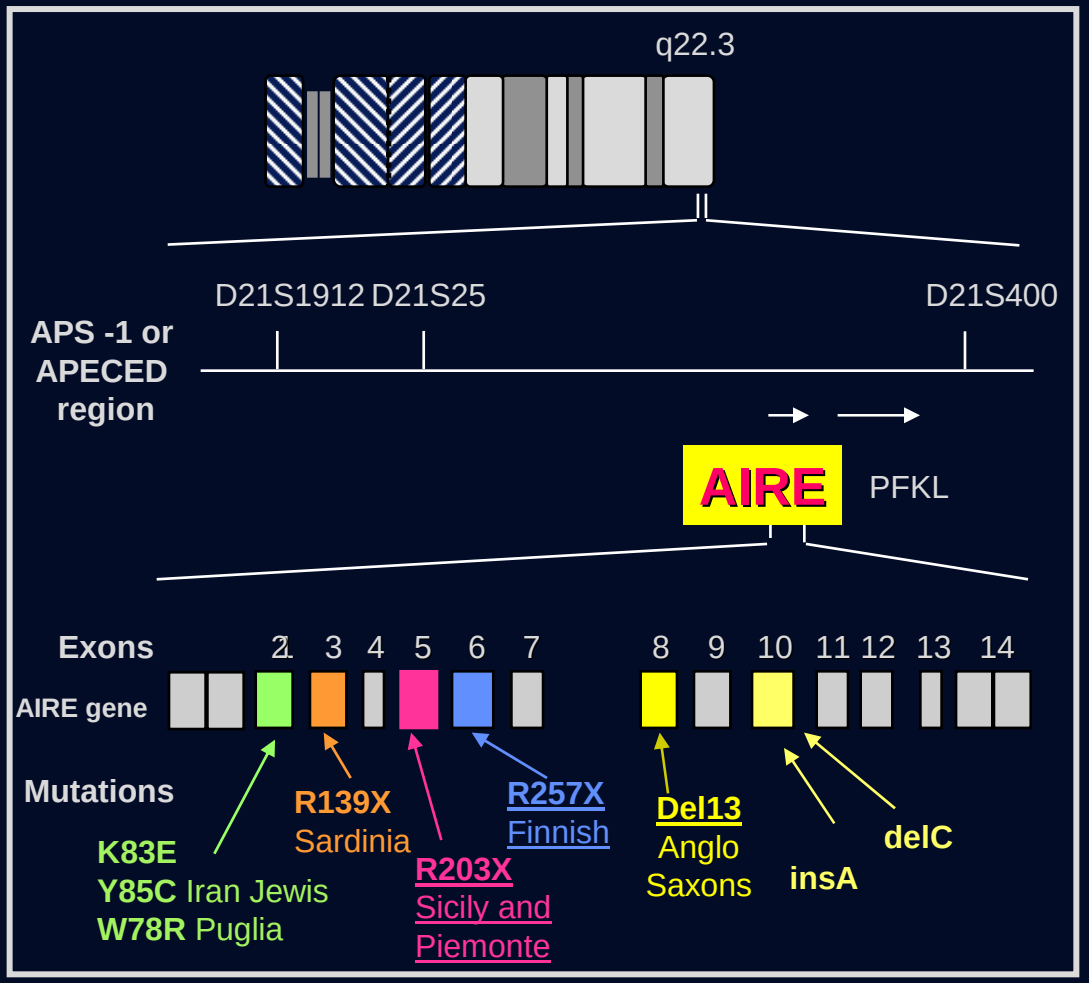


Cancer of tongue



GENETIC OF APS-1 In Italy

CHROMOSOME 21



Sindrome ad ereditarietà autosomica recessiva non legata al sesso dovuta a mutazioni a carico del gene AIRE (AutoImmune REgulator) posto sul cromosoma 21

K. Nagamine , Nat. Genet. 17: 393;1997
P. Peterson, Immunol.Today 19: 384;1998

AIRE GENE MUTATIONS in 23 Italian Patients with APECED

2nd EurAPS Meeting

Piedmonte Region
1 case R203x/R203x

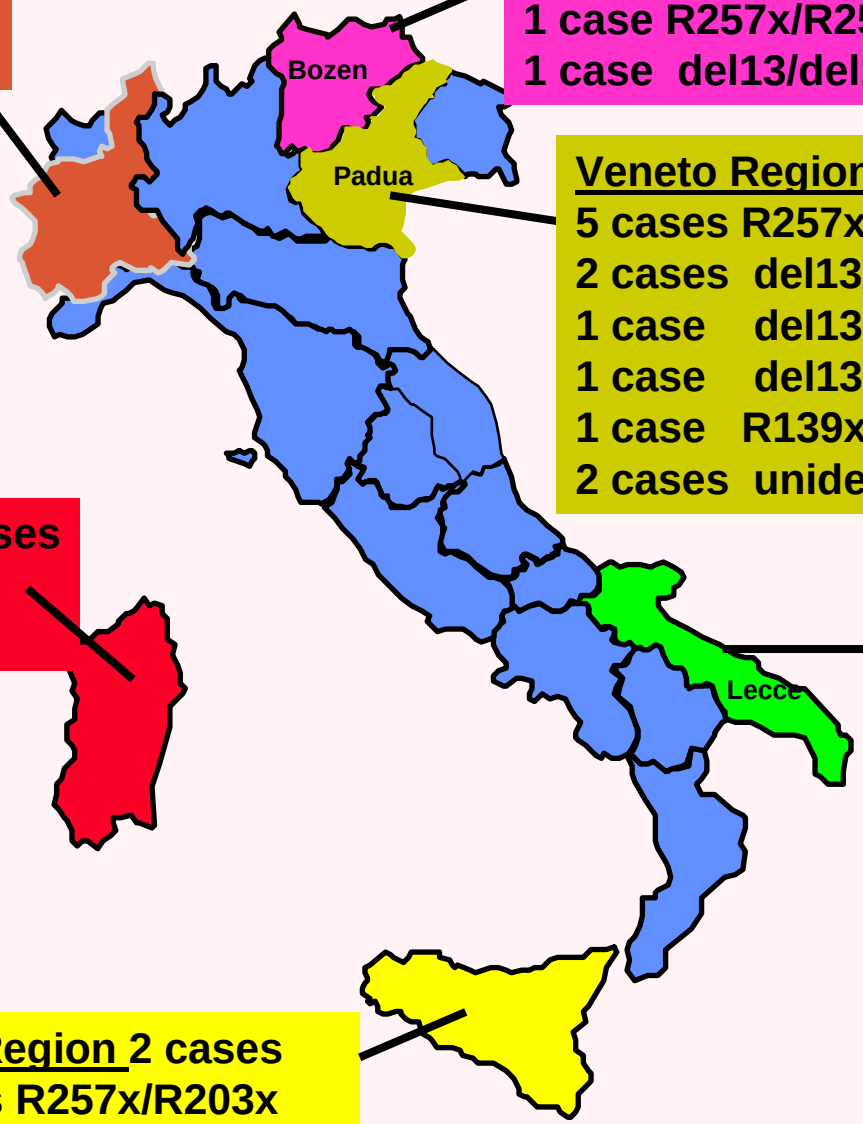
South Tyrol Region 2 cases
1 case R257x/R257x
1 case del13/del13

Veneto Region 12 cases
5 cases R257x/R257x
2 cases del13/R257x
1 case del13/del13
1 case del13/delGT^{1032}
1 case R139x/R139x
2 cases unidentified

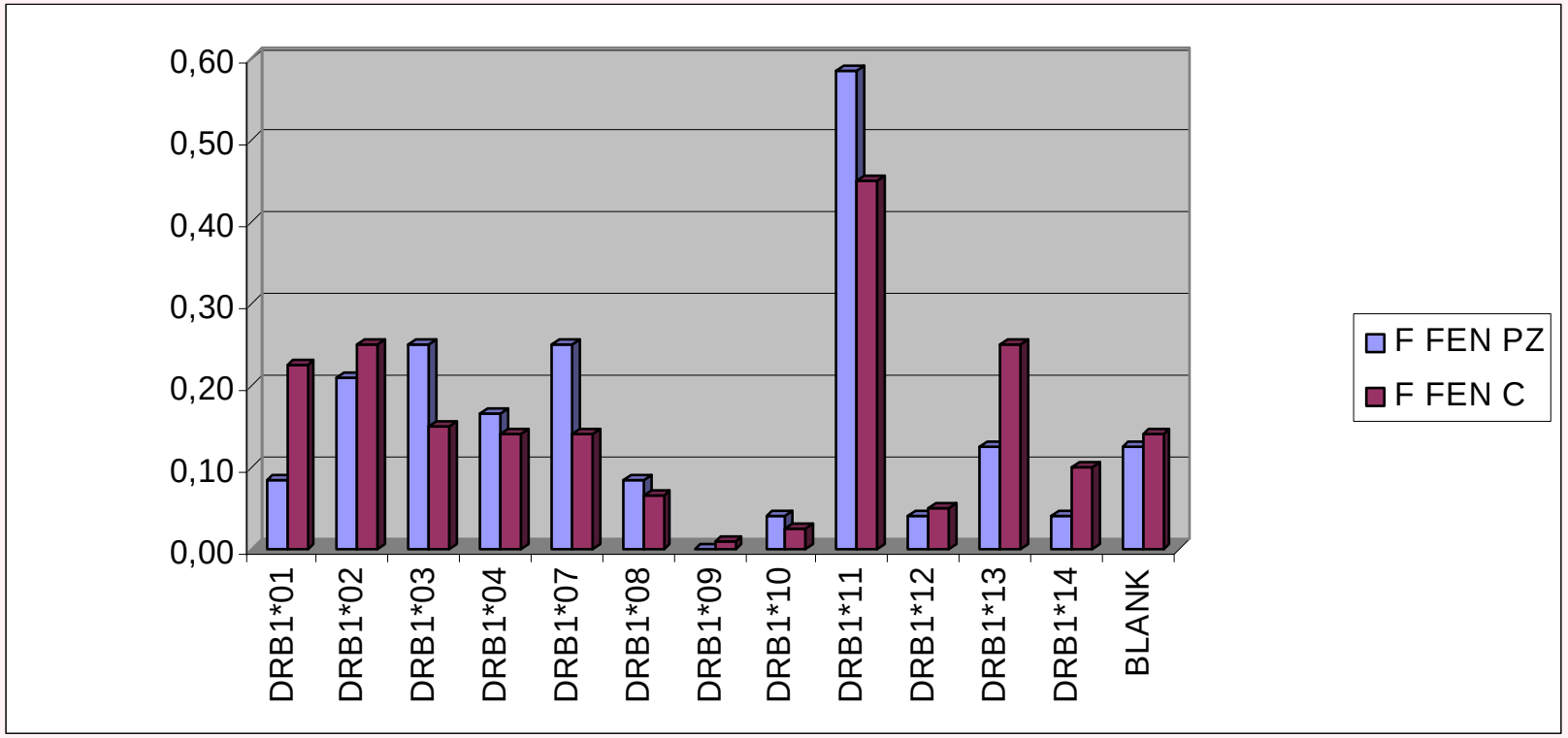
Sardinia Region 2 cases
1 case R139x/R139x
1 case R139x/del13

Apulia Region 4 cases
3 cases w78R/Q358x
1 case w78R/w78R

Sicily Region 2 cases
2 cases R257x/R203x



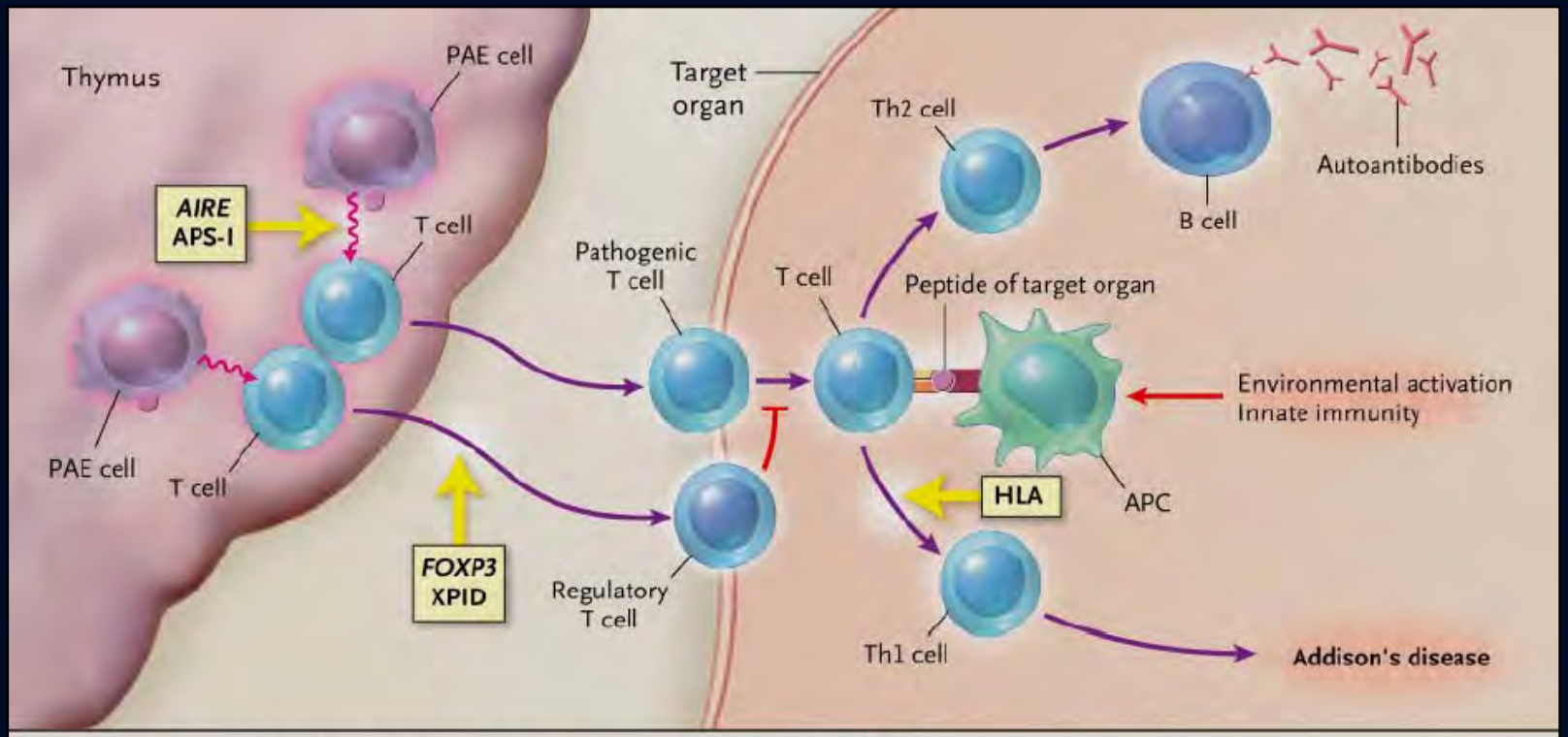
CLASS II HLA
in 24 Italian patients with APECED



Autoimmune Polyendocrine Syndromes

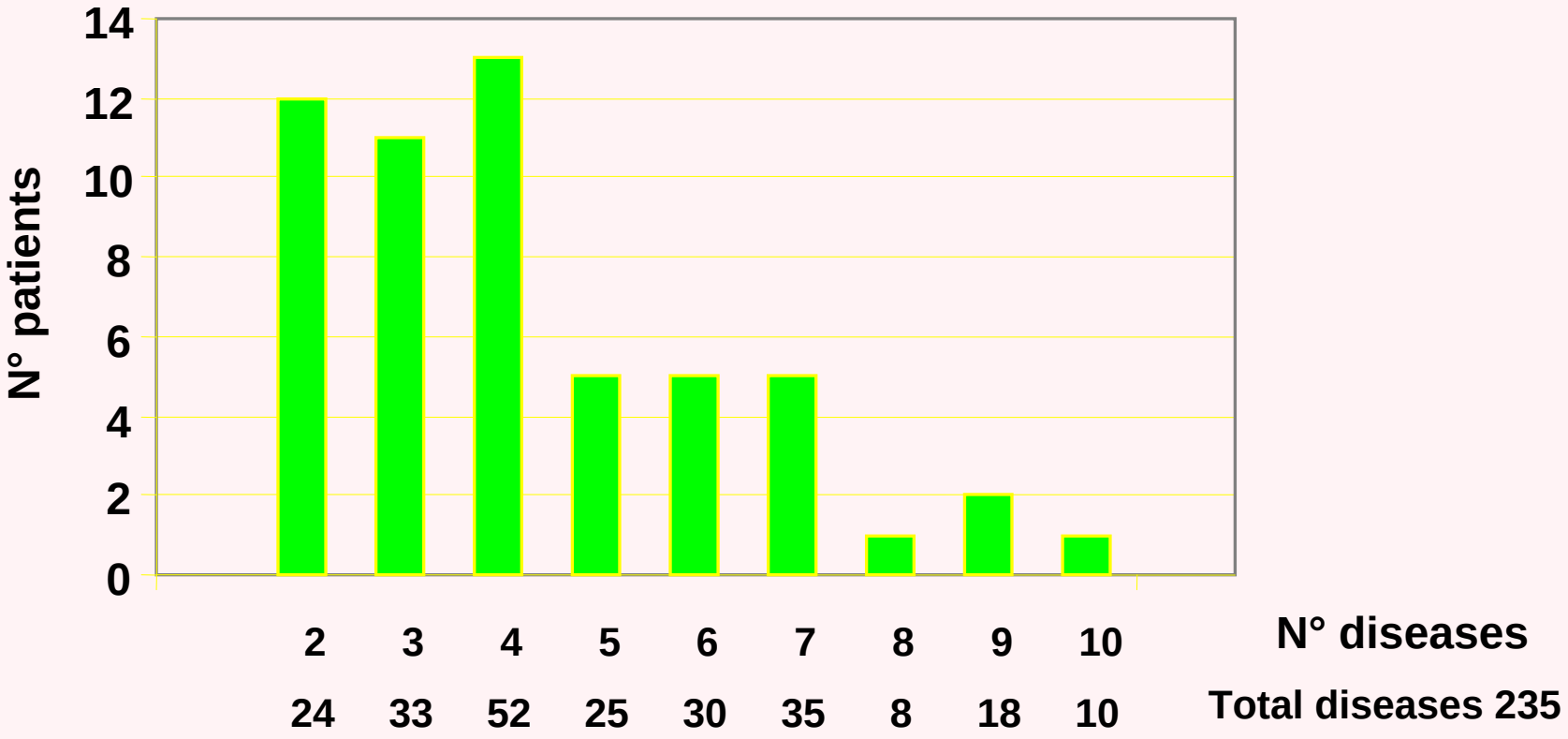
George S. Eisenbarth, M.D., Ph.D., and Peter A. Gottlieb, M.D.

N Engl J Med 2004;350:2068-79.



The presence of the AIRE mutated proteins may inhibit the apoptosis of autoreactive T lymphocytes at the thymic level, and these cells can precociously migrate at the peripheral level where they can initiate an autoimmune aggression in a very young age.

APS-1
235 diseases
in 55 cases



APS-2 (Schmidt's syndrome)

Addison's disease

+

Thyroid autoimmune diseases

and/or

Type 1 DM

+

other minor autoimmune diseases

FREQUENCY

15-40 cases / million

Autoimmune polyglandular syndrome Type 2: the tip of an iceberg?

Clin Exp Immunol 137:225;2004

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Table 3. Clinical features of patients with Type 2 APS

	From Neufeld *et al.* [56]	Personal data
Patients (no.)	224	146
Female/Male ratio	1·8	4
Family history of Type 2 APS	n.r.	0
Adults/Children	n.r.	133/13
Main diseases		
Addison's disease	100%	100%
Thyroid autoimmune diseases	69%	88%
Type 1 diabetes mellitus	52%	23%
Minor diseases		
Vitiligo	4·5%	12%
Hypergonadotropic hypogonadism	3·6%	10%
Chronic autoimmune hepatitis	n.r.	3%
Alopecia	0·5%	4%
Pernicious anaemia	<1%	2%
Seronegative arthritis	n.r.	2%
Myasthenia gravis	n.r.	0
Adenohypophysitis	n.r.	0

n.r., not reported.

Table 4. Prevalence of the main autoimmune diseases in Type 2 APS patients (personal data)

Endocrine diseases	No. of cases	Prevalence (%)
Addison's disease + chronic thyroiditis	82	56·1
Addison's disease + Graves' disease	31	21·2
Addison's disease + Type 1 diabetes mellitus	16	10·9
Addison's disease + chronic thyroiditis + Type 1 diabetes mellitus	14	9·6
Addison's disease + Graves' disease + Type 1 diabetes mellitus	3	2·0

Table 5. Ages of onset of the different autoimmune diseases in patients with Type 2 APS and frequency of the relevant antibodies

Autoimmune disease	Mean age at disease onset (years) (range)	Frequency of the relevant autoantibody at disease onset† (%)
Vitiligo	27·7 (9–43)	None
Type 1 diabetes mellitus	28·4 (2–63)	70
Hypergonadotropic hypogonadism	29·0 (18–40)	100
Graves' disease	33·4 (7–58)	80
Addison's disease	34·6 (1–85)	91
Pernicious anaemia	35·5 (34–37)	100
Alopecia	38·6 (32–52)	None
Chronic thyroiditis	40·2 (12–80)	97
Chronic atrophic gastritis	45·4 (16–65)	70
Autoimmune chronic hepatitis	51·6 (42–61)	100

†i.e. less than 1 years from the clinical diagnosis.

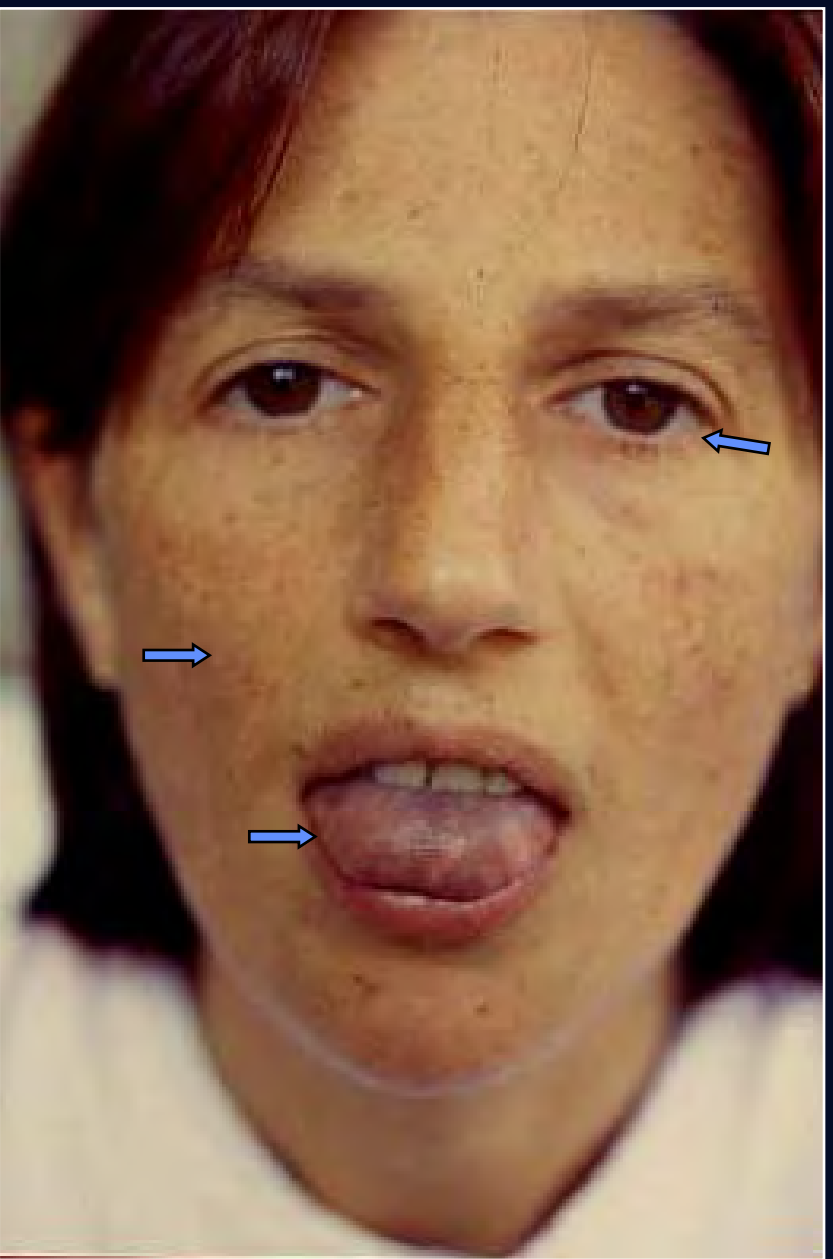
APS-2

Combinazione Familiare

Madre
T. Hashimoto

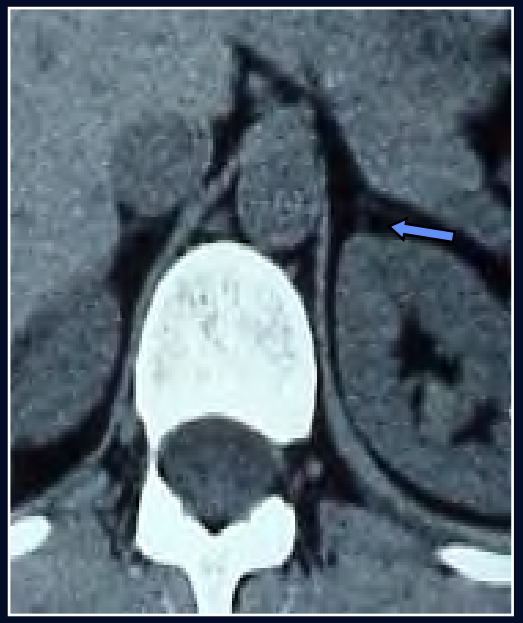
Figlia
M. di Addison

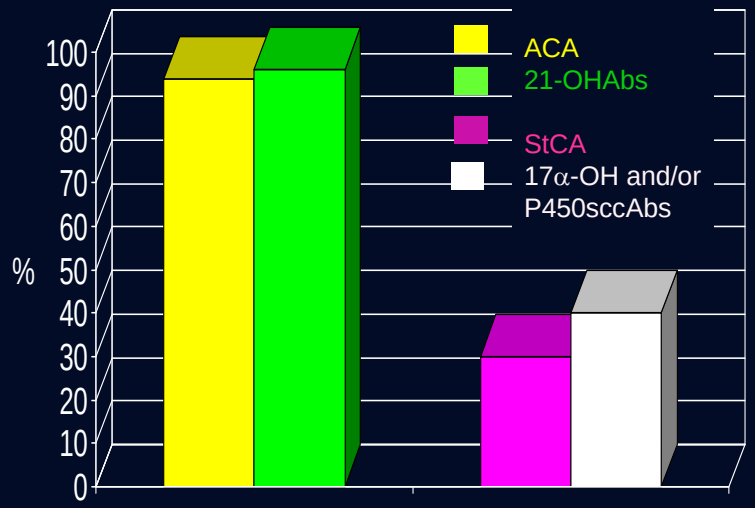
APS-2: Addison's disease: clinical, imaging, immunology



Pathology and imaging

The adrenal glands from patients with with AD is atrophic with lymphocytic infiltration but sometimes the adrenal tissue is not detectable



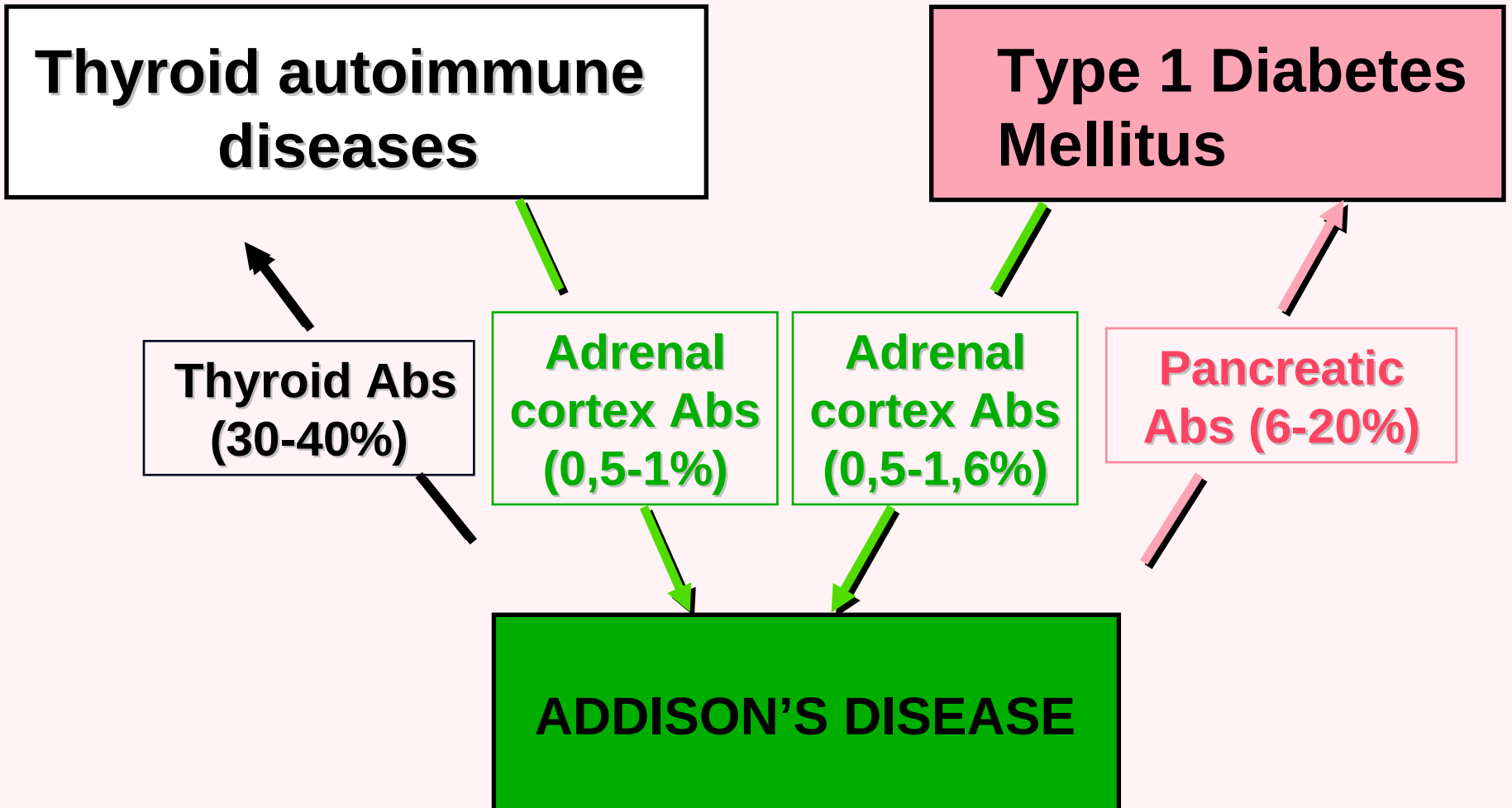


Can we predict

APS-2

in patients with one

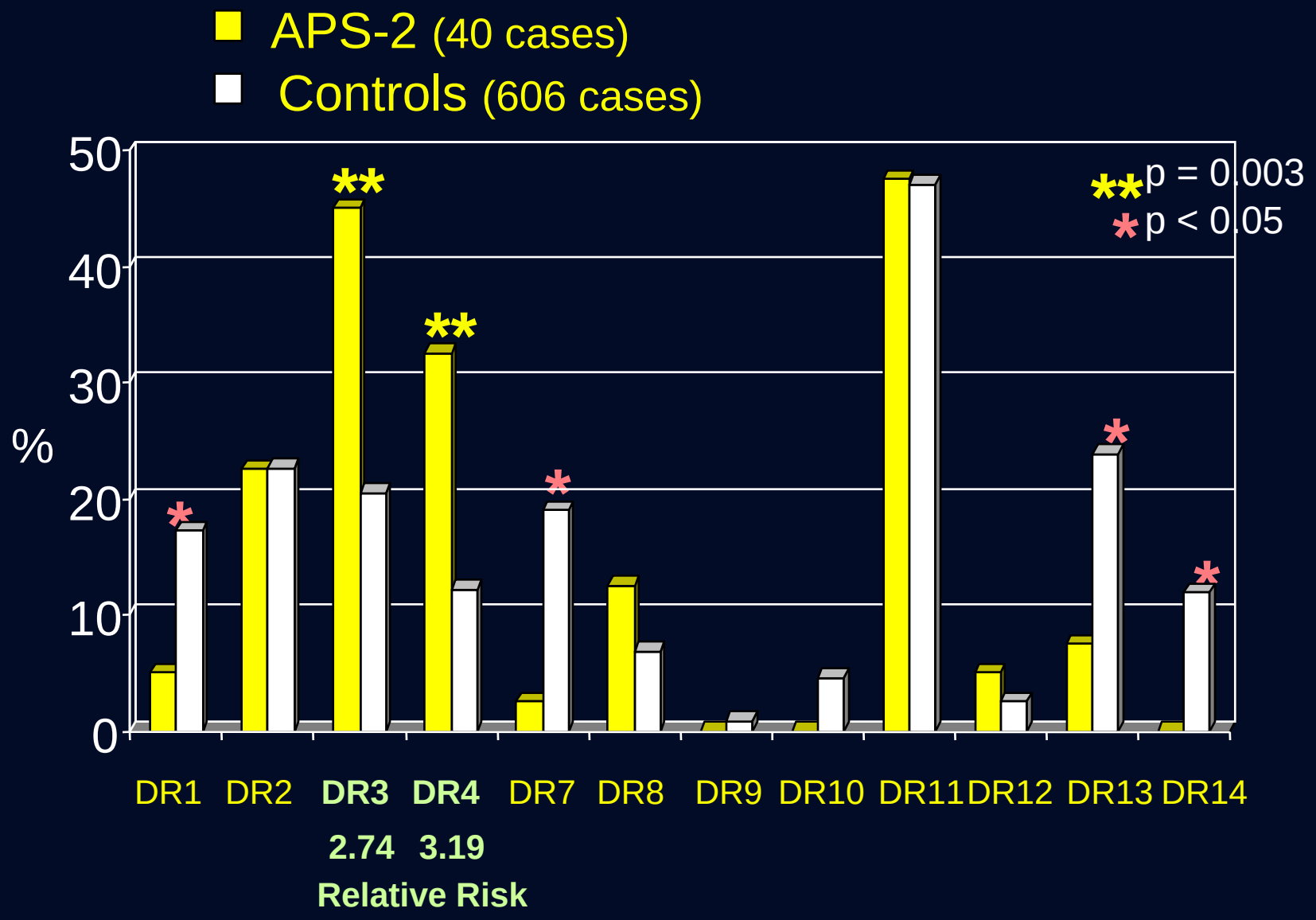
component of the Syndrome?



AUTOANTIBODIES IN APS-2

AT ONSET OF THE DISEASE	AUTOANTIBODIES TO	BEFORE DISEASE
Type 1 diabetes mellitus	Islet-cell (ICA), GADAbs, IA2-Abs	yes
Autoimmune thyroid diseases	Thyroperoxydase Abs, Thyroglobulin Abs, **TSH-R-Abs**	yes yes
Hypergonadotropic hypogonadism	steroid-producing cell (StCA), 17alfa-OHAbs, P450sccAbs	yes ? ?
Vitiligo	none	
Chronic active hepatitis	liver-kidney microsomal (LKM)	yes
Coeliac disease	Endomysium Abs Tranglutaminase Abs	yes yes
Chronic atrophic gastritis	parietal-cell (PCA)	yes
Pernicious anemia	PCA + intrinsic-factor (IFA)	yes
Alopecia areata	none	

GENETIC OF PATIENTS WITH APS-2



CHARACTERISTICS OF ITALIAN PATIENTS WITH APS-1 AND APS-2

	APS-1 (n= 55)	APS-2 (n= 146)
Hypoparathyroidism	89 %	--
Mucocutaneous candidiasis	84	--
Addison's disease	82	100 %
Autoimmune Thyroid Diseases	18 %	88 %
DM Type 1	7.0	52 %
Hypergonadotr. Hypogonadism	22 %	10%
Alopecia	35	4
Chronic hepatitis	22	3
Vitiligo	22	12
Chronic atrophic gastritis	15	11
Pernicious anemia	15	2
Malabsorption	9	0
Myasthenia gravis	0	0
Neoplasias	6	3
Female/male ratio	1.7	4.0
Adult/Children ratio	0.08	10
Genetic	AIRE gene mutations	DR3/DR4

Betterle et al. Endocrine Reviews 23: 327; 2002

APS-3

THYROID AUTOIMMUNE DISEASES (TAD)

Hashimoto's thyroiditis

Symptomless autoimmune thyroiditis

Idiopathic mixedema

Graves' disease

\+ \+ \+

3A	3B	3C
Type 1 DM	Atrofic gastritis Pernicious anemia	Vitiligo Alopecia Myasthenia gravis

Neufeld & Blizzard 1980

APS-3

288 cases of thyroid autoimmune diseases

3.A Type 1 Diabetes mellitus
Premature menopause
Lymphocitic hypophysitis
Diabetes Insipidus
hypoparathyroidism
3.B Chronic atrophic gastritis
Pernicious anemia
Coeliac disease
Inflammatory bowel diseases
Autoimmune hepatitis
Primary biliary cirrhosis
3.C Vitiligo
Alopecia
Myasthenia gravis
Multiple sclerosis
Stiff-man syndrome
Werlhof's disease
3.D SLE/LED
Sjögren's syndrome
Sistemic sclerosis
Rheumatoid arthritis
Ankylosis spondilitis
Antiphospholipid syndrome
Multiple Sclerosis
15-20%

positive for one or more autoantibody
15-20%

negative for clinical autoimmune diseases or for autoantibodies
60-70%

Clinical APS 3

Latent APS 3

Isolated AITD

Prevalenza SPA-3

Tiroiditi	croniche	SPA 3
Femmine	10%	3%
Maschi	3%	1%

SPA-3 (classificazione 2002)

(Betterle et al. Endocrine Reviews 23: 327; 2002)

TIREOPATIE AUTOIMMUNI

Tiroidite di Hashimoto
Mixedema idiopatico
Tiroidite asintomatica

Esoftalmo endocrino
Mixedema pretibiale

Morbo di Graves

+	+	+	+
DM Tipo 1 Sindrome di Hirata Menopausa precoce Adenoipofisite Neuroipofisite Ipoparatiroidismo	Gastrite atrofica Anemia perniciosa Morbo celiaco M. Infiam. Cr. Intest. Cirrosi biliare Epatite cronica Colangite sclerosante	Vitiligine Alopecia Miastenia Gravis Sclerosi multipla Sindrome di Stiff-man Atassia con GADAbs Sindrome di Guillain-Barrè Citopenie autoimmuni	LES/LED Artrite reumatoide Connettivite mista Artriti Sieronegative Sindrome di Sjögren Sclerosi Sistemica S. da antifosfolipidi Vasculiti
Endocrinopatie 3A	Apparato GI, Fegato, 3B	Cute, Muscolo, S. N., S. Emopoietico 3C	Collagenopatie, Vasculiti 3D

SPA-3 SUBCLINICA O LATENTE

TIREOPATIE AUTOIMMUNI

Tiroidite di Hashimoto
Mixedema idiopatico
Tiroidite asintomatica

Esoftalmo endocrino
Mixedema pretibiale

Morbo di Graves

+	+	+	+
ICA/GADAbs/ IA2Abs Anti-cellule producenti steroidi (StCA) Anti-ipofisi Anti-diencefalo Anti-sensori del Ca+	PCA PCA + IFA Anti-endomisio Anti-tranglutaminasi Anti-mitocondrio ANTI-LKM ANCA	Anti-R-Ach Anti-GAD Anti-Purkinjie Anti-mielina Anti-piastrine	ANA/DNAn Fattore Reumatoide Anti-citrullina Anti-SSA/SSB Anti-ENA Anti-fosfolipidi ANCA
Endocrinopatie 3A	Apparato G.I. e Fegato 3B	Cute, Muscolo, S.N., S. Emopoietico 3C	Collagenopatie Vasculiti 3D

SPA-3 SUBCLINICA O LATENTE

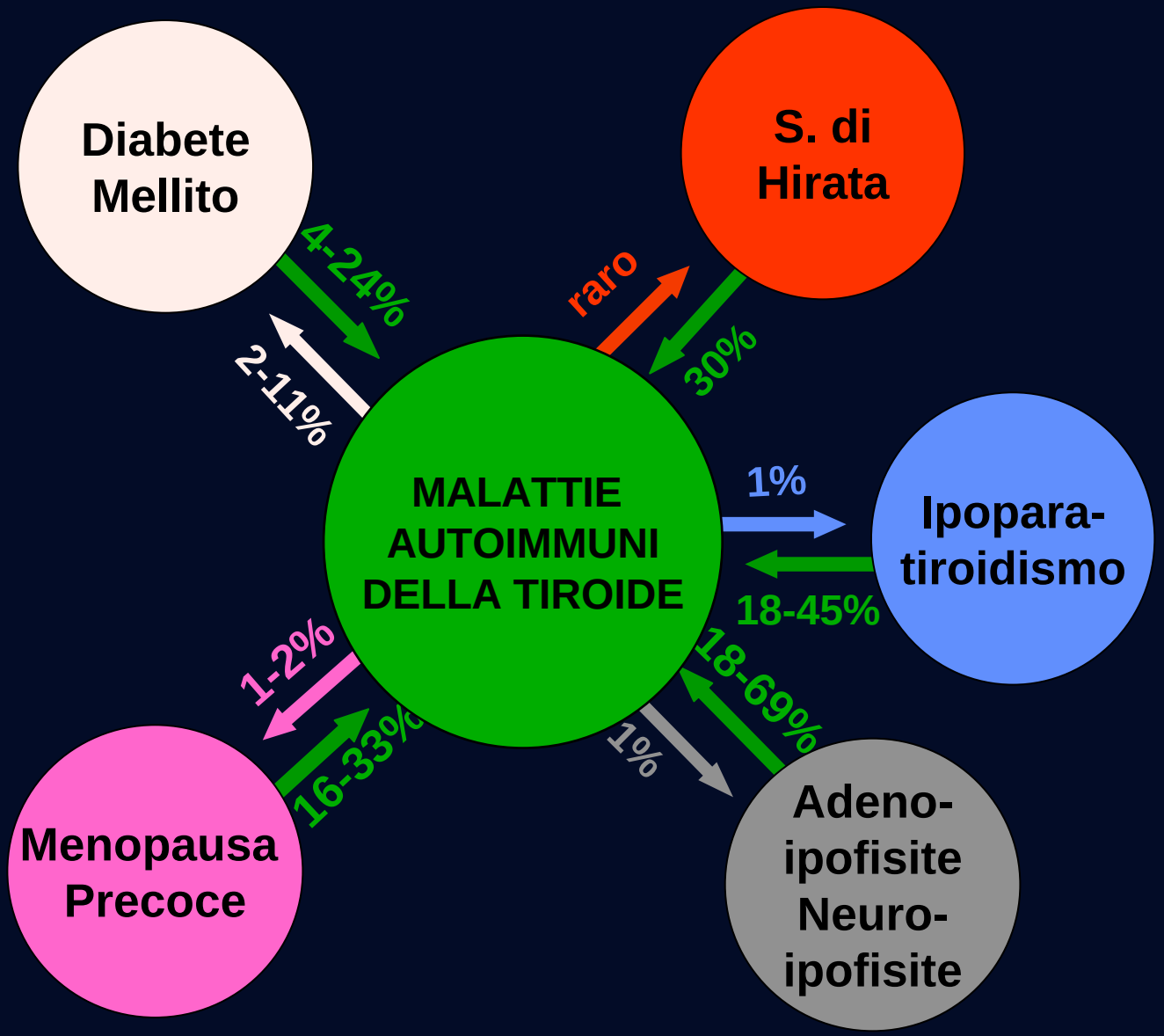
Anticorpi anti-tiroidite (10-50%)

+	+	+	+
DM Tipo 1 Sindrome di Hirata Menopausa precoce Adenoipofisite Neuroipofisite Ipoparatiroidismo	Gastrite atrofica Anemia perniciosa Morbo celiaco M. Infiam. Cr. Intestino Cirrosi biliare Epatite cronica Colangite sclerosante	Vitiligine Alopecia Miastenia Gravis Sclerosi multipla Sindrome di Stiff-man Atassia con anti-GAD Sindrome di Guillain-Barrè Citopenie autoimmuni	LES/LED Artrite reumatoide Connettivite mista Sindrome di Sjögren Artriti sieronegative Sclerosi Sistemica S. da antifosfolipidi Vasculiti
Endocrinopatie 3A	Apparato G.I., Fegato, 3B	Cute, Muscolo, SN, S. Emopoietico 3C	Collagenopatie, Vasculiti 3D

Patients with Type 1 DM: frequency of TAD

Year	Authors	N° of patients	Age	Thyroid antibodies only	Clinical hypo-thyroidism	Clinical hyper-thyroidism	Subclinical thyroid dysfunction	Total AITD
1963	Moore	33	adults	15.0%	3.0%			18.0%
1970	Goldstein	155	children	8.0%				
1970	Irvine	671	all ages	17.5%				
1973	Nerup	66	not reported	17.0%				
1980	Neufeld	504	children	17.0%				
1982	Court	134	children/adults	10.4%	2.2%			12.6%
1982	Kokkonen	84	12-19 years	11.9%	0%			11.9%
1984	Gilani	58	1-18 years	12.0%	3.5%			15.5%
1985	MacLaren	1.456	all ages	23.0%	n.d.	n.d.	n.d.	
1987	Drell	3.779	not reported	17.9%	n.d.	n.d.	n.d.	
1990	Kontiainen	133	children	24.0%	n.d.	n.d.	n.d.	24.0%
1992	Landin-Ollson	473	15-34 years	5.0%	n.d.	n.d.	n.d.	
1995	Radetti	1.419	children	2.5%	0.07%	0.07%	1.3%	3.9%
1995	Perros	406	adults	n.d.	10.5%	4.2%	8.1%	
1995	Abrams	157	10-39 years	17.1%	n.d.	n.d.	n.d.	
1996	Jefferson	974	children		2.2%	0.2%	n.d.	
1997	Presotto	1.741	all ages	11.8%	0.8%	1.6%	n.d.	14.1%
1998	Mccanlies	265	children		15.1%	9.3%	11.5%	
1999	Hansen	105	children	13.3%	0.9%		1%	15.2%
1999	Roldan	204	<20 years	-	-	-	-	17.6%
2001	De Block	399	all ages	17.0%	4.0%	3.0%	n.d.	24.0%
2002	Kordonouri	7.097	Children/ adolescents	21.6%	n.d.	n.d.	n.d.	21.6%
	All cases	20.109		2.5-24%	0-15.1%	0.07-9.3%	1-11.5%	4-24%

TAD + MALATTIE AUTOIMMUNI ENDOCRINE = SPA 3A



TAD E M. AUTOIMMUNI DEL FEGATO E DEL TRATTO G.I.= SPA 3B

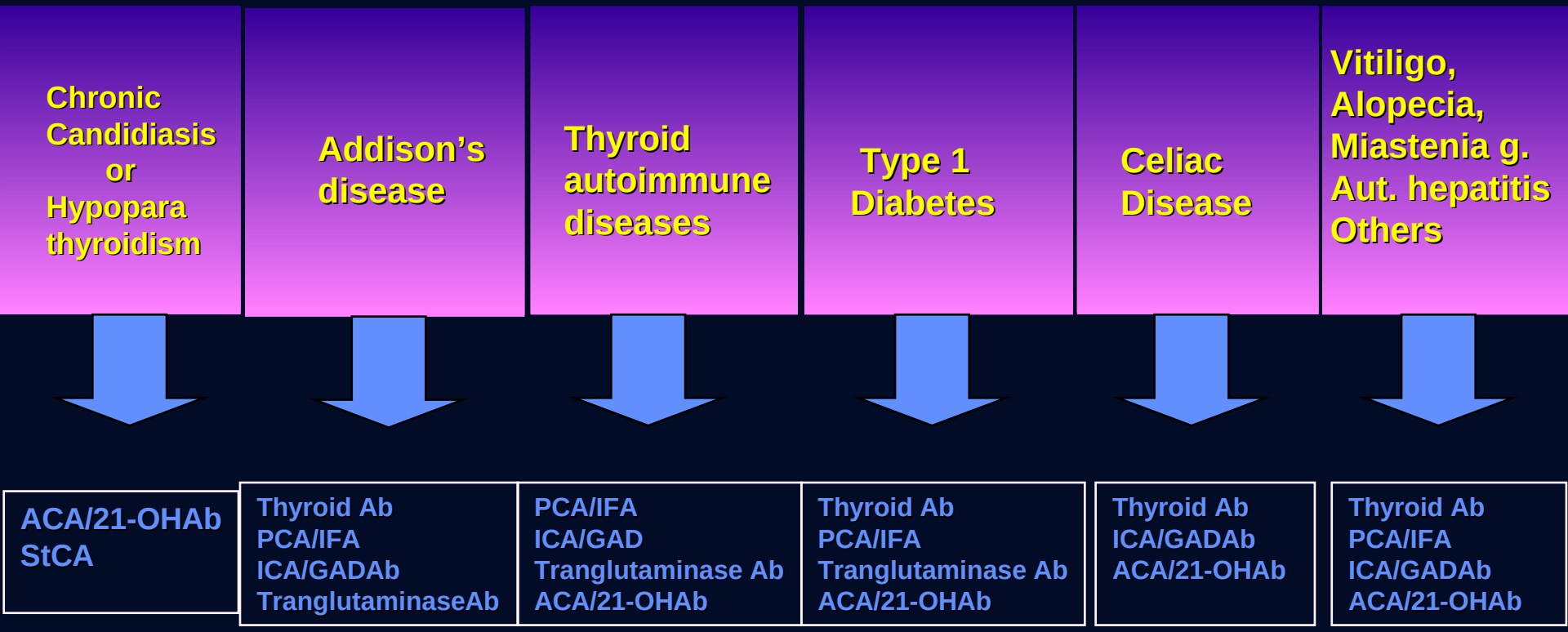
SPA-4

Ogni Combinazione che non rientri nella SPA-1,-2,-3

Esempi

Vitiligo	Type 1 Diabetes	Type 1 Diabetes	Vitiligo	Celiac disease	Vitiligo
+	+	+	+	+	
Atrophic gastritis	Atrophic gastritis	Celiac disease	Alopecia	Atrophic gastritis	Ipoparati-roidismo

Proposta di screening autoanticorpale nei pazienti con singola malattia autoimmune per scoprire quelli con SPA subclinica o potenziale



3th AACE-AME Joint Meeting
2006, October 27-29, Verona

WHEN and HOW to ASSESS Autoimmune Endocrinopathies

Rinaldo Guglielmi

Regina Apostolorum Hospital

Albano Laziale (Rome)

Autoimmune Polyglandular Syndromes (APS)

	APS-1	APS-2	APS-3
Age at Onset	Childhood (peak <10 yrs)	Adult (peak 30 yr)	Adult (peak 30 yr)
Genetics	AIRE gene, with component diseases influenced by HLA-DR/DQ genotype	Primarily DR3, DR4 and others in specific diseases	Primarily DR3, DR4 and others in specific diseases
Clinical Manifestations			
Addison's disease	++	++	-
Hypoparathyroidism	++	-	
Chronic Mucocutaneous Candidiasis	++	-	-
Graves' Disease	-	+	+
Hashimoto's Thyroiditis	+/-	++	++
Pernicious Anemia	+ (early onset)	+	++ (late onset)
T1DMA	+/-	++	+
Gonadal Failure	++ (Females)	+/-	+/-
Vitiligo	+	+	+
Chronic Active Hepatitis	+	-	-
Alopecia	+ (universalis)	-	-
Malabsorption	+	-	-
Celiac Disease	+	+	+
Hypopituitarism	+	+/-	-
Myasthenia gravis	-	+/-	+/-

Autoimmune Polyglandular Syndromes (APS)

	APS-1	APS-2	APS-3
Age at Onset	Childhood (peak <10 yrs)	Adult (peak 30 yr)	Adult (peak 30 yr)
Genetics	AIRE gene, with component diseases influenced by HLA-DR/DQ genotype	Primarily DR3, DR4 and others in specific diseases	Primarily DR3, DR4 and others in specific diseases
Clinical Manifestations			
Addison's disease	++	++	-
Hypoparathyroidism	++	-	
Chronic Mucocutaneous Candidiasis	++	-	-
Graves' Disease	-	+	+
Hashimoto's Thyroiditis	+/-	++	++
Pernicious Anemia	+ (early onset)	+	++ (late onset)
T1DMA	+/-	++	+
Gonadal Failure	++ (Females)	+/-	+/-
Vitiligo	+	+	+
Chronic Active Hepatitis	+	-	-
Alopecia	+ (universalis)	-	-
Malabsorption	+	-	-
Celiac Disease	+	+	+
Hypopituitarism	+	+/-	-
Myasthenia gravis	-	+/-	+/-

Autoimmune Polyglandular Syndromes (APS)

	APS-1	APS-2	APS-3
Age at Onset	Childhood (peak <10 yrs)	Adult (peak 30 yr)	Adult (peak 30 yr)
Genetics	AIRE gene, with component diseases influenced by HLA-DR/DQ genotype	Primarily DR3, DR4 and others in specific diseases	Primarily DR3, DR4 and others in specific diseases
Clinical Manifestations			
Addison's disease	++		-
Hypoparathyroidism	++	-	
Chronic Mucocutaneous Candidiasis	++	-	-
Graves' Disease	-	+	+
Hashimoto's Thyroiditis	+/-	++	++
Pernicious Anemia	+ (early onset)	+	++ (late onset)
T1DMA	+/-	++	+
Gonadal Failure	++ (Females)	+/-	+/-
Vitiligo	+	+	+
Chronic Active Hepatitis	+	-	-
Alopecia	+ (universalis)	-	-
Malabsorption	+	-	-
Celiac Disease	+	+	+
Hypopituitarism	+	+/-	-
Myasthenia gravis	-	+/-	+/-

Clinical queries

1) What is the clinical impact of the diseases?

2) In cost-effective terms, which single component of the syndrome should be screened?

3) What should be the initial evaluation in order to exclude or confirm the syndrome?

4) How wide should be the clinical assessment of the syndrome?

5) What kind of follow up in patients at risk?

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The prevalence of APS type 1 is very low

Data are widely variable

Most frequencies are from 1/80.000
to 1/ 9.000 inhabitants

In Sardinia: 1/25.000 inhabitants

In Italy about 4/1.000.000.000

APS type 2 is a rare condition

From 1.4 to 2/100.000 inhabitants

APS2/APS1 ratio: 5/1

APS type 3 and 4 are a very rare condition

No definitive data of prevalence available

Betterle et all, End Rev, 2002

Clinical queries

1) What is the clinical impact of the diseases?

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The prevalence of Addison's disease in Coventry, UK.

Willis AC, Vince FP.

Coventry and Warwickshire Hospital, West Midlands, UK.

The prevalence of Addison's disease (chronic adrenal failure) has not been widely investigated and is usually given as 39 in a million. We conducted a prevalence study using a postal survey of general practitioners in Coventry. Three quarters (139/188) replied, representing 79/85 (93%) of the practices. Thirty cases of Addision's disease were found from a total patient list of 323852, of which a third were tuberculous in origin and two-thirds non-tuberculous (12/30 autoimmune, 8/30 unclassified). **We conclude that Addison's disease is 2.4 times more common than previously reported**. The tuberculous group was older, 65 vs 52 years ($p < 0.05$), and had had the disease for longer than the non-tuberculous group, 20 vs 12 years ($p < 0.05$). There was no significant difference in the age at diagnosis.

Postgrad Med J. 1997 May;73(859):286-8.

Is the Prevalence of Addison's Disease Underestimated?

… adrenal autoantibodies are present in 70% of Addison patients (2). Furthermore, approximately 1% of patients with endocrine autoimmune disorders have clinical or subclinical signs of adrenal insufficiency (3). In initial studies (4, 5), the prevalence of Addison's disease in Western countries was calculated at 35–60 per million. However, the results of a recent study (6) suggest that this disease could be more common than previously reported.
… selected a geographically delimited region of central Italy, Umbria, and we determined the total number of subjects suffering from Addison's disease, during the period January 1–December 31, 1996 in this region. According to the Italian Institute of Statistics (ISTAT), the population resident in Umbria is 811,887 (394,211 males and 417,676 females).

…95 (42 males and 53 females) Addison patients…

..the resulting prevalence of Addison's disease in the general population was **117 per million** (95% confidence interval: 95–143).
Prevalence among males and females was 106 per million (95% confidence interval: 77–144) and 127 per million (95% confidence interval: 95–166), respectively.
The frequency of Addison's disease in our study represents the highest prevalence reported so far, and it is 2- to 3-fold higher than those previously reported in other studies (4, 5).

Our results indicate that the prevalence of Addison's disease has so far been underestimated. Given the increase in frequency of adrenal autoimmunity in Addison patients observed over the last 20 years, we hypothesize that the incidence and prevalence of autoimmune adrenal insufficiency is rising. Additional population-based studies are needed to monitor the yearly incidence of this disease and to test this latter specific hypothesis.

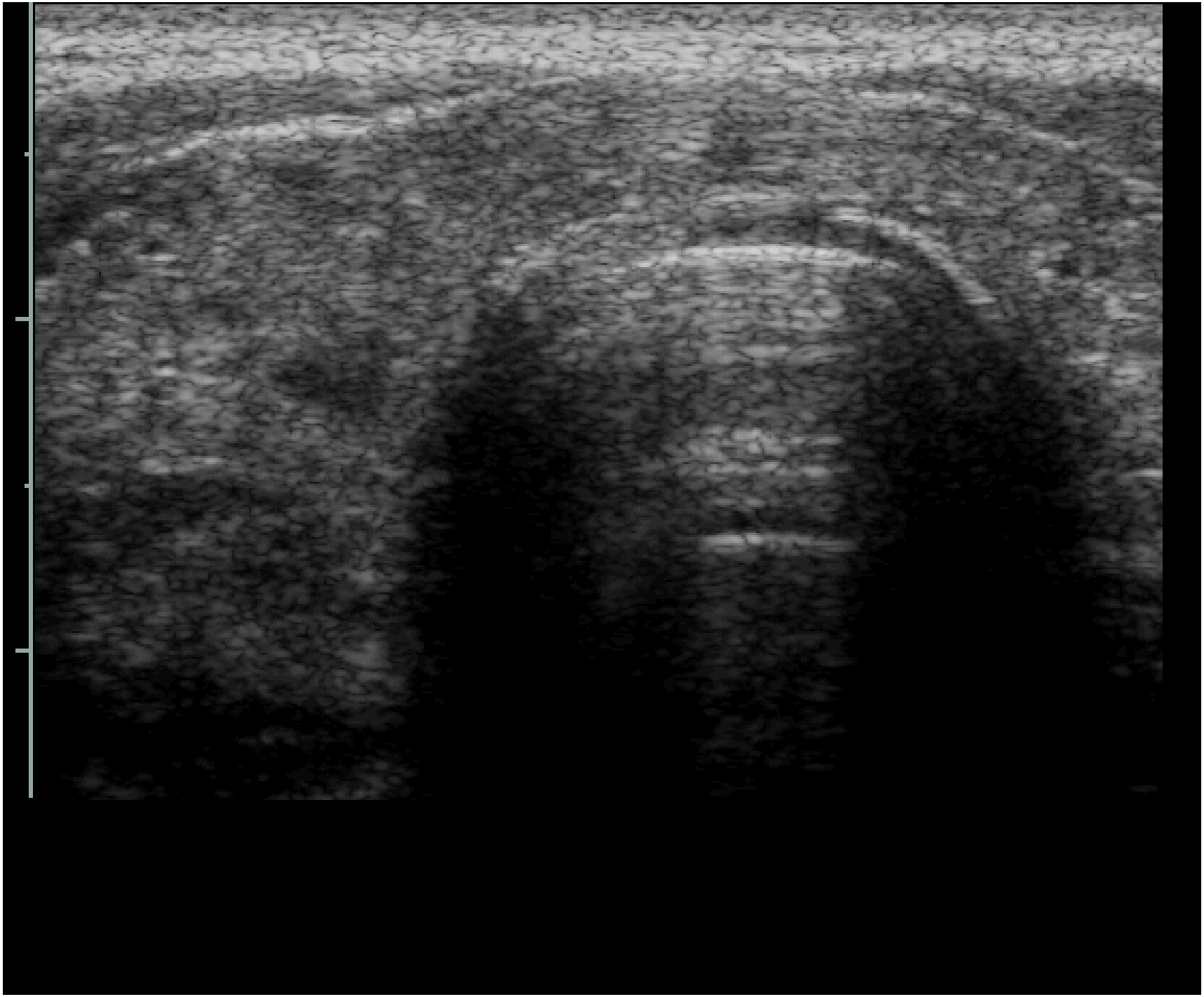
Laureti et all, JCEM 1999

Prevalence of Diagnosed Diabetes in People Aged 20 Years or Younger, United States, 2005

About 176,500 people aged 20 years or younger have diabetes. This group represents 0.22 percent of all people in this age group.

About one in every 400 to 600 children and adolescents has type 1 diabetes.

National Diabetes Information Clearinghouse, 2005



Prevalence of chronic autoimmune thyroiditis in the urban area neighboring a petrochemical complex and a control area in Sao Paulo, Brazil.

Camargo RY, Tomimori EK, Neves SC, Knobel M, Medeiros-Neto G.

PURPOSE: ..... From the Polo Area, in the vicinity of a large petrochemical industrial complex, 409 subjects were included; from the control area (Sao Bernardo Campo Area) 420 individuals were included. .....

RESULTS: Chronic autoimmune thyroiditis was diagnosed both echographically (marked hypoechogenicity) and immunologically (presence of autoantibodies against thyroid peroxidase). In the Polo Area, 15.6% of the examined population had chronic autoimmune thyroiditis, and in the control area (Sao Bernardo Campo Area), 19.5% of the population had evidence of chronic autoimmune thyroiditis (P > 0.057, not significant). The prevalence of hypothyroidism was 4.9% in the Polo Area and 8.3% in the Sao Bernardo Campo Area (P = 0.0461 significant). .....

CONCLUSION: The high iodine intake (above 300 microg Iodine/L of urine) that was present from 1998 through 2005 may be related to a higher prevalence of chronic autoimmune thyroiditis in both areas that were studied. There was no apparent or documented relationship of chronic autoimmune thyroiditis prevalence to the proximity to the petrochemical complex

Clinics. 2006 Aug;61(4):307-12

The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey.

Aghini-Lombardi F, Antonangeli L, Martino E, Vitti P, Maccherini D, Leoli F, Rago T, Grasso L, Aleriano R, Balestrieri A, Pinchera A.

We carefully assessed thyroid status and goiter by ultrasound in **1411 subjects** virtually representing the entire resident population of Pescopagano, an iodine-deficient village of Southern Italy. Median urinary iodine excretion was 55 microg/L. The prevalence of goiter was 16.0% in children and 59.8% in adults. Thyroid nodularity was 0.5% in children and progressively increased with age to 28.5% in the 56- to 65-yr-old group. The prevalence of present or past hyperthyroidism was 2.9%, including 9 cases with toxic diffuse goiter and 20 with toxic nodular goiter. Functional autonomy was rare in children, progressively increased with age up to 15.4% in the elderly, and was related to nodular goiter. The prevalences of overt and subclinical hypothyroidism in the adults were 0.2% and 3.8%, respectively. **Serum autoantibodies to thyroglobulin and thyroperoxidase were detected in 12.6% of the entire population.** The prevalence of diffuse autoimmune thyroiditis was 3.5%, being very low in children. Thyroid cancer was found in only 1 case. In conclusion, in the present survey of an iodine-deficient community, a progressive increase with age of goiter prevalence, thyroid nodularity, and functional autonomy was observed. Hyperthyroidism was twice as high as that reported in iodine-sufficient areas, mainly due to an increased frequency of toxic nodular goiter. Although low titer serum thyroid antibodies were relatively frequent, the prevalences of both overt and subclinical autoimmune hypothyroidism were not different from those observed in iodine-sufficient areas.

J Clin Endocrinol Metab. 1999 Feb;84(2):561-6.

Prevalence of idiopathic hypoparathyroidism and pseudohypoparathyroidism in Japan.

Nakamura Y et all.

A nationwide epidemiologic survey of idiopathic hypoparathyroidism and pseudohypoparathyroidism was conducted in 1998 to clarify the prevalence of the two disorders in Japan. From a total of 14,100 departments of pediatrics, internal medicine, neurology, and endocrinology in whole Japan, 2952 (20.9%) study departments were selected at random. Of these departments receiving the first questionnaire, 1855 (62.8%) responded. From these departments 390 patients with idiopathic hypoparathyroidism and 203 with pseudohypoparathyroidism who visited the hospitals in 1997 were reported. The total numbers of patients were estimated to be 900 (690-1100) for idiopathic hypoparathyroidism and 430 (330-520) for pseudohypoparathyroidism (95% confidence intervals in parentheses). Using these data, the period prevalence of the diseases were **7.2 (5.5-8.8) per million population in idiopathic hypoparathyroidism**, and 3.4 (2.6-4.2) in pseudohypoparathyroidism (95% confidence intervals in parentheses).

J Epidemiol. 2000 Jan;10(1):29-33

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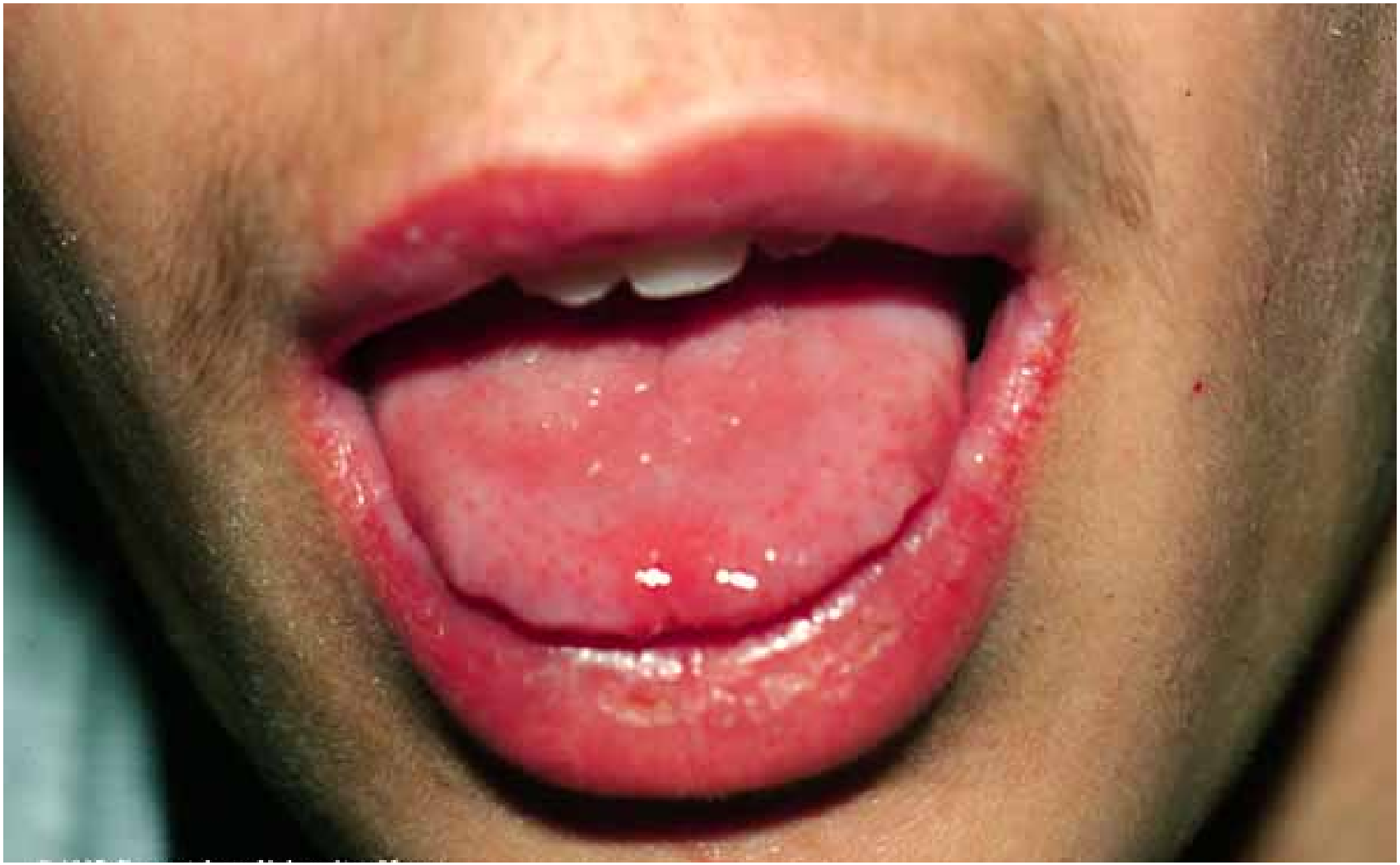
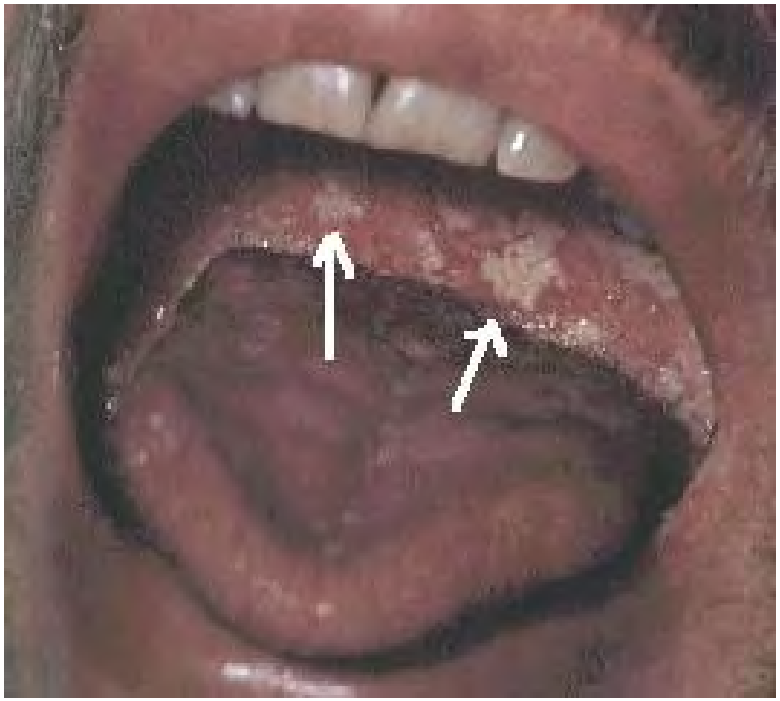
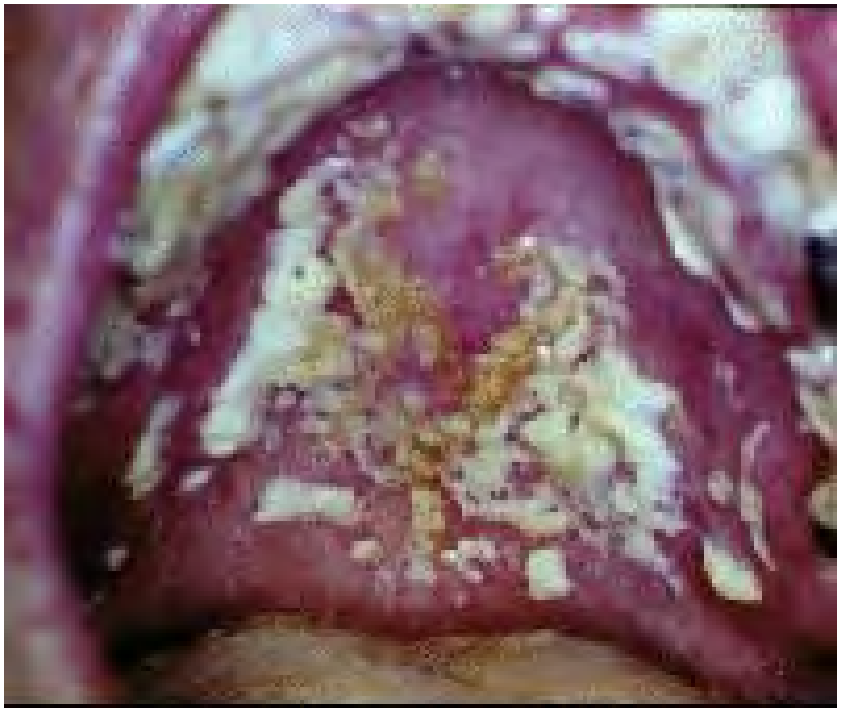
Oral Candidiasis



Oral Candidiasis





International surveillance of bloodstream infections due to Candida species: frequency of occurrence and in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY antimicrobial surveillance program.

Pfaller MA, Diekema DJ, Jones RN, Sader HS, Fluit AC, Hollis RJ, Messer SA; SENTRY Participant Group.

A surveillance program (SENTRY) of bloodstream infections (BSI) in the United States, Canada, Latin America, and Europe from 1997 through 1999 detected 1,184 episodes of candidemia in 71 medical centers (32 in the United States, 23 in Europe, 9 in Latin America, and 7 in Canada). Overall, 55% of the yeast BSIs were due to Candida albicans, followed by Candida glabrata and Candida parapsilosis (15%), Candida tropicalis (9%), and miscellaneous Candida spp. (6%). ……Both ravuconazole and voriconazole were significantly more active than fluconazole against C. glabrata (MIC(90)s of 0.5 to 1.0 microg/ml versus 16 to 32 microg/ml, respectively). A trend of increased susceptibility of C. glabrata to fluconazole was noted over the three-year period. The percentage of C. glabrata isolates susceptible to fluconazole increased from 48% in 1997 to 84% in 1999, and MIC(50)s decreased from 16 to 4 microg/ml. A similar trend was documented in both the Americas (57 to 84% susceptible) and Europe (22 to 80% susceptible). Some geographic differences in susceptibility to triazole were observed with Canadian isolates generally more susceptible than isolates from the United States and Europe. These observations suggest susceptibility patterns and trends among yeast isolates from BSI and raise additional questions that can be answered only by continued surveillance and clinical investigations of the type reported here (SENTRY Program).

***Candida* was the fourth-most-common nosocomial BSI isolate category**

J Clin Microbiol. 2001 Sep;39(9):3254-9.

	Prevalence	disease/ APS1 ratio prevalence ratio	disease/ APS2 ratio prevalence ratio
Addison disease	9-14/100.000 (Willis 2006)	30/1	6 / 1
T1DMA	1 / 400-600 (NDIC 2005)	500 / 1	100 / 1
Thyroiditis/ Graves	5 to 15/100 (Aghini-Lombardi 1999)	25.000/1	5.000/1
Hypo - parathyroidism	7/1.000.000 (Nakamura 2000)	1.5/1	1/3
Mucocutaneous Candidiasis	fourth-most-common nosocomial BSI isolate category	-----	-----

Prevalence: 1-2% worldwide

1,059,560 people in the USA 1996

Rose and Mackay, 1998, The Autoimmune Diseases, Third Edition

Vitiligo prevalence study in Shaanxi Province, China

Tao Lu et all

Background Recent publications, especially those based on population surveys, show that the presumed vitiligo prevalence of 1–2% is overestimated.

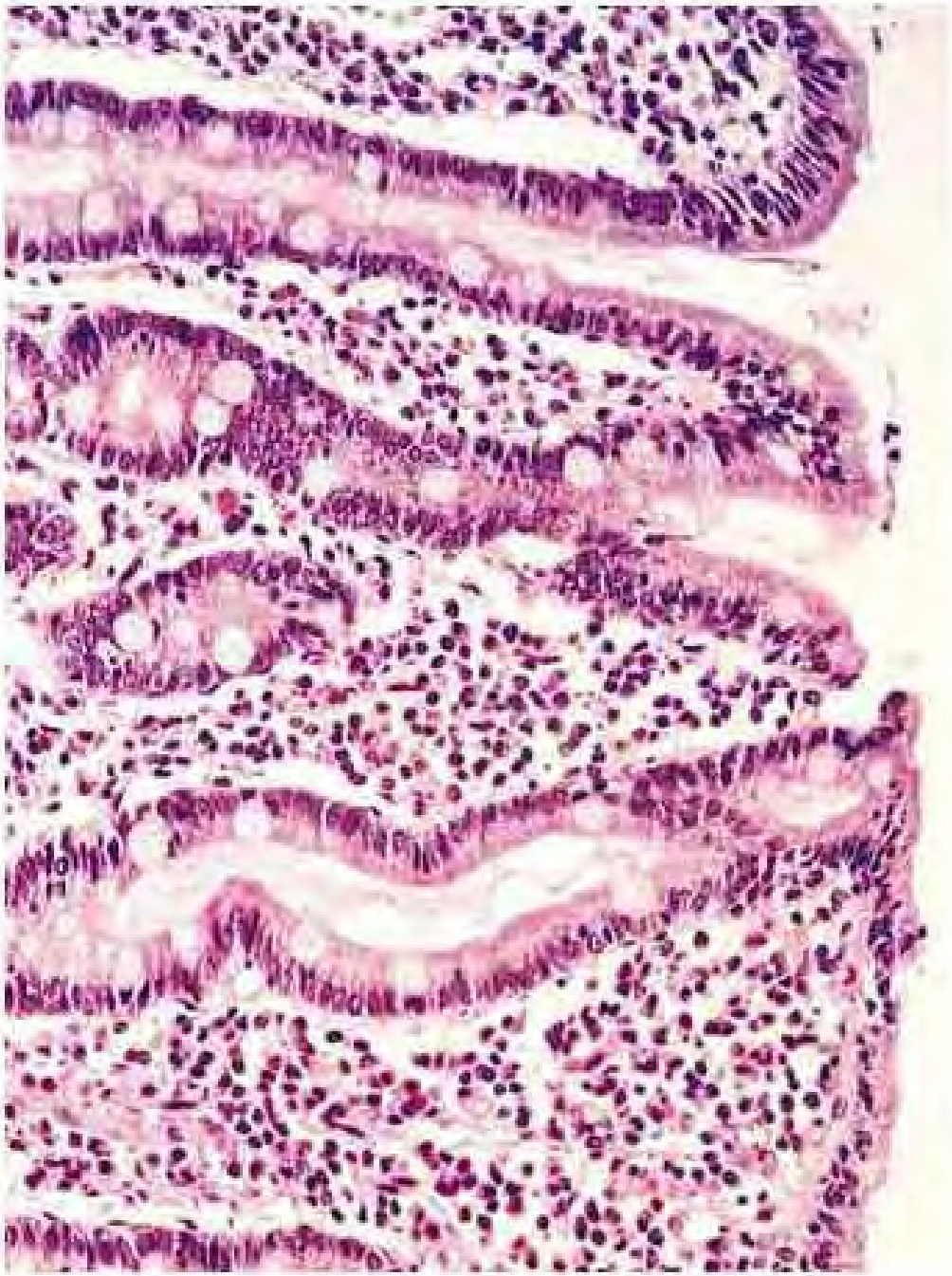
Objective To obtain the vitiligo prevalence in Shaanxi Province, China, through a population survey.

Methods Approximately one-thousandth of the 36.05 million people in Shaanxi Province, China, were selected through stratified four-stage cluster sampling. They lived in 180 investigation units and all were investigated in a door-to-door survey. Vitiligo and suspected vitiligo patients were marked in the basic questionnaire. They were encouraged to complete a well-prepared questionnaire and send it back to the investigation center. The questionnaire assigned to the investigators contained questions about vitiligo characteristics, such as the area affected, number of areas, and whether or not the affected areas were covered by scurf. Professional dermatologists verified these results.

Results There were 42,833 people in 180 investigation units. The sex, residence, and educational level of these individuals were representative of the population of Shaanxi Province. The investigation team reported 43 vitiligo patients and 14 with suspected vitiligo. During the verification period, three patients and all those with suspected vitiligo were excluded. In total, there were 40 patients (17 women and 23 men). Eleven lived in urban areas and 29 in rural areas.

Conclusions The **prevalence** of vitiligo in Shaanxi Province is **0.093%** (95% confidence interval, 0.067–0.127%). No significant difference was found between males and females or between urban and rural residents.

International Journal of Dermatology
Online Early
doi:10.1111/j.1365-4632.2006.02848.x



CELIAC DISEASE

1 in 250 Americans
estimated rate

1 in 250 in Italy

1 in 300 in Ireland

TIP OF ICEBERG

Actual diagnosis rate is
1 in 4,700 Americans

Less than 1/15 cases
diagnosed

Reader's Digest Feb 2004

Adult coeliac disease: prevalence and clinical significance.

Cook HB et all

BACKGROUND AND AIMS: Although coeliac disease is a common condition, the role of population screening is not clear. The aim of this study was to determine the prevalence and clinical significance of coeliac disease in the adult population of Christchurch, New Zealand. METHODS: A total of 1064 adults randomly selected from the 1996 Christchurch electoral rolls were enlisted. The subjects were screened for coeliac disease using the anti-endomysial antibody test (EMA), and all those with positive tests were reviewed and underwent a small bowel biopsy. RESULTS: Twelve of the 1064 persons tested (1.1%) were EMA positive and all had small bowel biopsy histology consistent with coeliac disease. Two of the 12 subjects were previously known to be EMA positive although neither had a small bowel biopsy. One additional subject with known and treated coeliac disease was also enrolled but was EMA negative. Thus, the overall **prevalence** of coeliac disease was **13 of 1064 subjects** (1.2%, or 1:82), 10 of whom were newly diagnosed (0.9%, or 1:106) and three were previously known or suspected to have coeliac disease (0.3%, or 1:355). The prevalence in both sexes was similar. Nine of the 12 EMA-positive coeliac disease subjects identified by the use of screening reported symptoms, of which tiredness and lethargy were the most common. The subjects were of normal stature, although females tended to be lean. None of the subjects were anaemic, but four were iron deficient and four folate deficient. Five of the 12 had sustained bone fractures. Bone mineral density was reduced in males but not in females. CONCLUSIONS: The prevalence of coeliac disease in the adult population of Christchurch, New Zealand, is 1.2%. Unrecognized coeliac disease which was detected by population screening was three-fold more common than proven or suspected coeliac disease. Population screening may identify subjects who could benefit from treatment.

J Gastroenterol Hepatol. 2000 Sep;15(9):1032-6

	Prevalence	disease/ APS1 prevalence ratio	disease/ APS2 ratio prevalence ratio
Vitiligo	1/100	2.500/1	500/1
Celiac Disease	1/250	1.000/1	200/1
Myastenia gravis	14/100.000	----	7/1
Pernicious Anemia	1/680 0.15% in USA	375/1	75/1
Gonadal Failure	2/100.000 (4-18% n 30-40 yrs old women)	5/1	1/1

Clinical queries

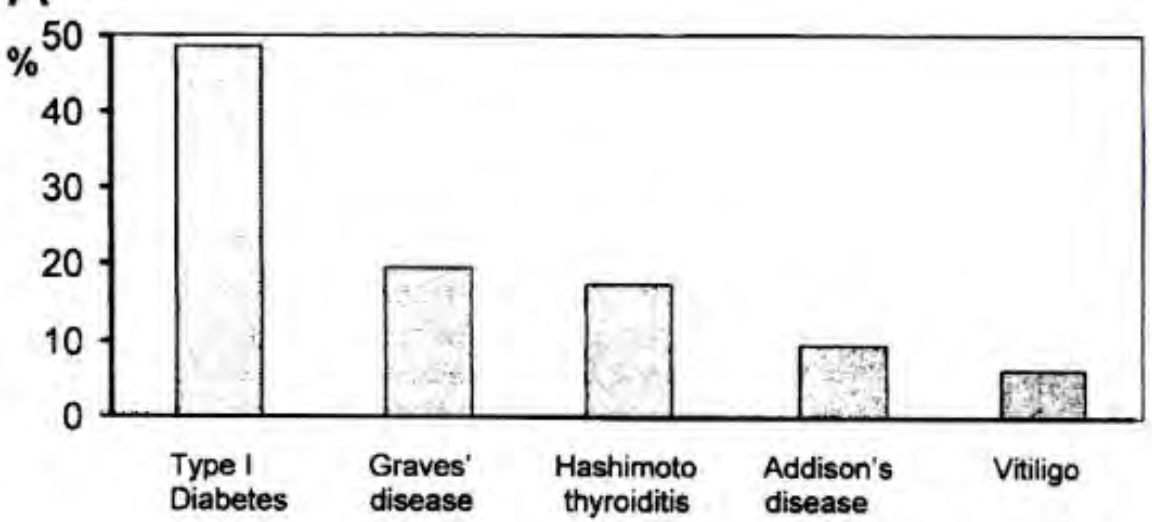
1) What is the clinical impact of the diseases?

2) In cost-effective terms, which single component of the syndrome should be screened?

3) What should be the initial evaluation in order to exclude or confirm the syndrome?

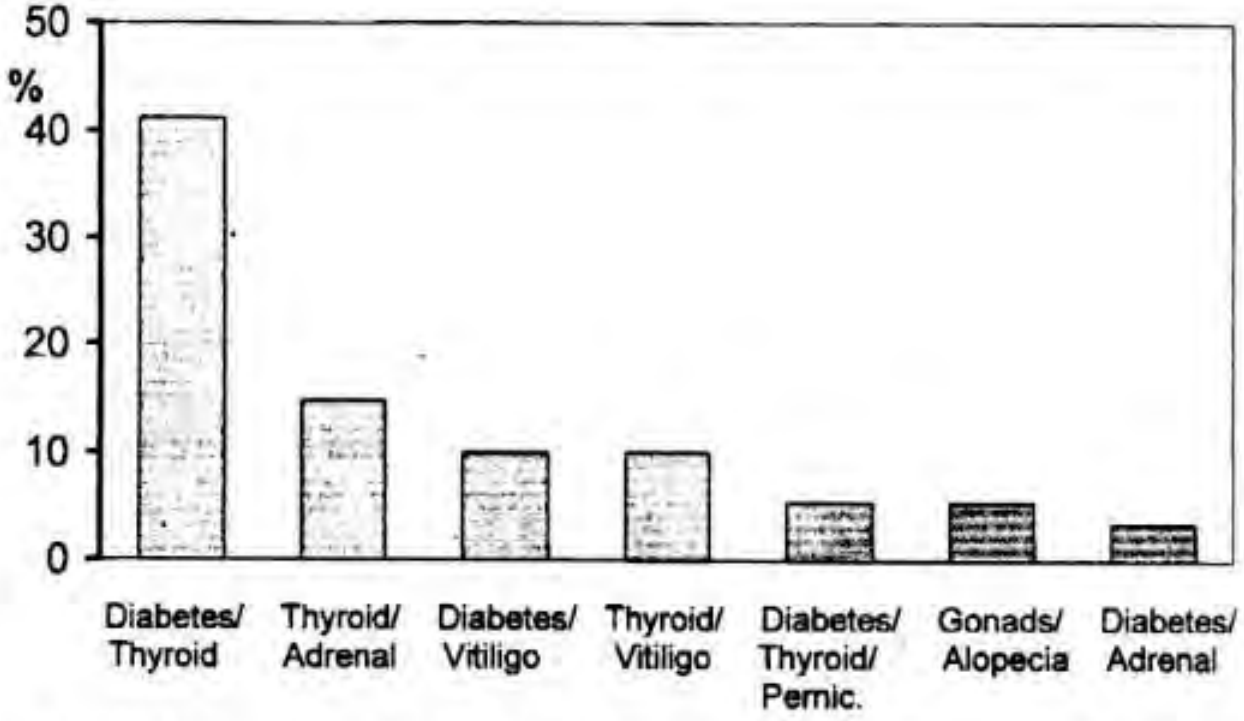
4) How wide should be the clinical assessment of the syndrome?

5) What kind of follow up in patients at risk?



First disease manifestation in patients with PAS II

Dittmar M and Kahaly GJ, JCEM
2003, 88(7):2983-2992



Most frequent disease combinations in patients with PAS II

Type 1 diabetic patient

Thyroid autoimmune disease:

TSH, TPO, US examination

TRAb, if presence of specific symptoms and/or low/suppressed plasma level of TSH

Vitiligo:

clinical cutis examination

Specific Ab assay if hypopigmented Areas are present

Type 1 diabetic patient

Pernicious Anemia :

hemochrome, serum B12 assay, LDH,APCA

Celiac disease:

tTG A (tTG G)

Intestinal biopsy if serum level:

>4 IU/ml (ELISA Eurospital)

High specificity when serum level >21 IU/ml

Diamanti et all, Pediatric in press

Type 1 diabetic patient

Adrenal Gland function:

Cortisol, ACTH,PRA, ACA and/or 21OH Ab

Diagnosis of Addison if

Baseline cortisol plasma level: < 3 mcg/dl

Normal function if value is >19 mcg/dl

Abdominal TC when functional diagnosis has been made

Adrenal stimulation with ACTH if:

Baseline cortisol plasma level: < 19 mcg/dl

and ACTH plasma level within the normal range

If cortisol < 19 mcg/dl and elevated ACTH level: Subclinical Hypoadrenalism

Patient at risk

Diabetes type 1 screening :

GAD Ab, plasma glycemia, OGTT/IVTT

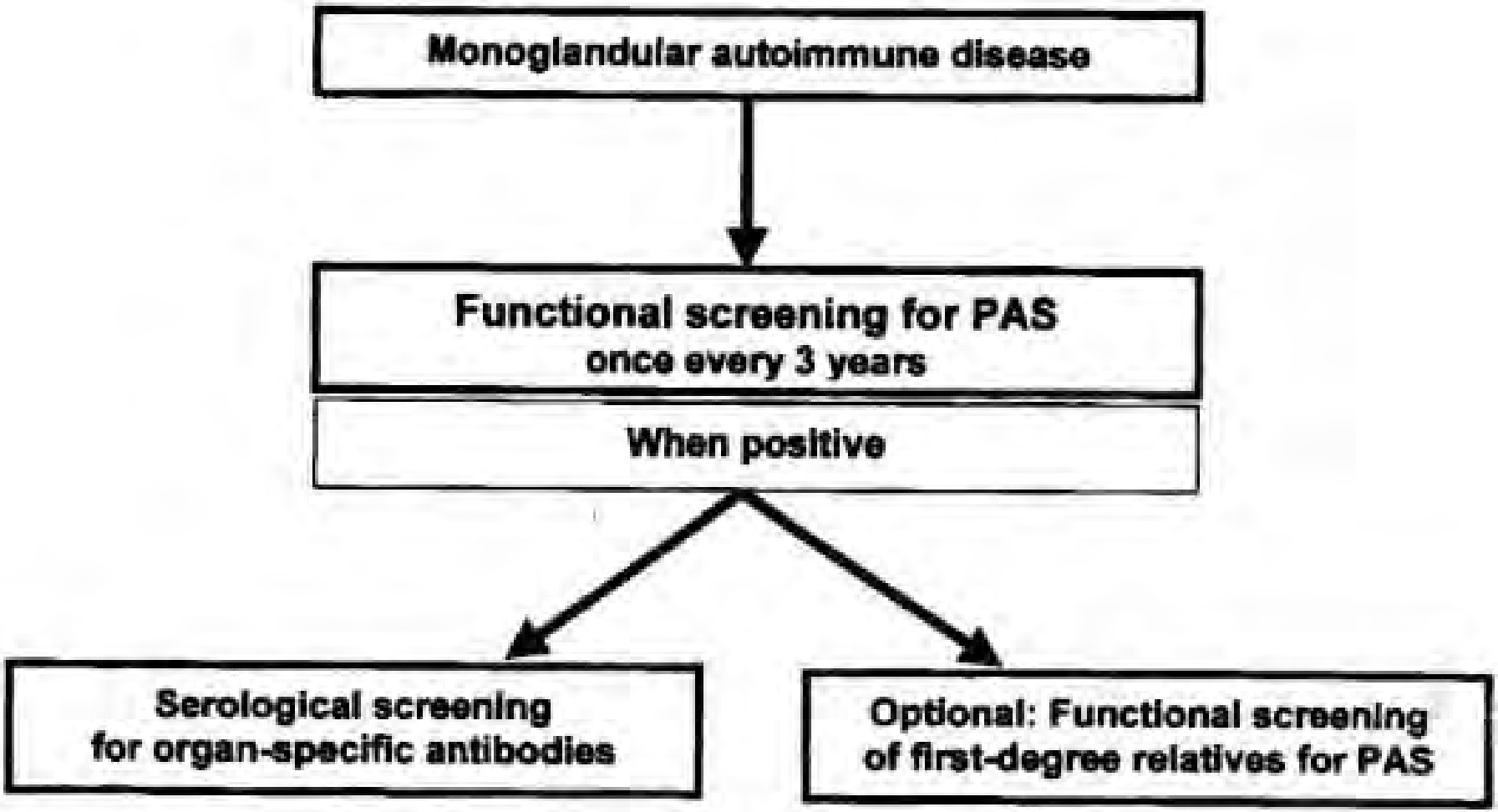


FIG. 6. Recommendations for screening of PAS type II.

Dittmar M and Kahaly GJ, 2003, 88(7):2983-2992

Clinical queries

1) What is the clinical impact of the diseases?

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5) What kind of follow up in patients at risk?

Eur J Endocrinol. 2006 Feb;154(2):275-9.

Celiac disease in North Italian patients with autoimmune Addison's disease.

Betterle C et all

OBJECTIVE: ……... DESIGN: The aim was to define the prevalence of CD and of IgA deficiency in a group of Italian patients with AAD. METHODS: One hundred and nine patients with AAD were enrolled and examined for tissue transglutaminase autoantibodies of the IgA class, circulating levels of IgA and adrenal cortex antibodies. RESULTS: Two (1.8%) of the patients were affected by already diagnosed CD and were already on a gluten-free diet. Out of the remaining 107 patients, four (3.7%) were found to be positive for IgA antibodies to human tissue transglutaminase. Three of the four patients who were positive for tissue transglutaminase autoantibodies agreed to undergo endoscopy and duodenal biopsies and, in one, a latent form of CD was identified. The clinical, silent or latent form of CD was present in six out of 109 (5.4%). This prevalence was significantly higher (P = 0.0001) than that reported for the Northern Italian population which was equal to 0.063%. Specifically, CD was present in 12.5% of the autoimmune polyglandular syndrome (APS) type 1 cases, in four out of 60 (6.7%) of the APS type 2 cases and in one out of 40 (2.5%) of the isolated AAD cases. ……. CONCLUSIONS: In patients with AAD there is a high prevalence of both CD and IgA deficiency. Consequently, it is important to screen for CD with tissue transglutaminase autoantibodies of the IgA class and for IgA levels.

Coeliac disease in patients with type 1 diabetes mellitus and auto-immune thyroid disorders.

Buysschaert M. Brussels, Belgium.

The paper aims to review the prevalence and natural history of coeliac disease in patients with type 1A diabetes mellitus and autoimmune thyroid disorders. These diseases share a similar genetic background. In diabetic children and adults, the prevalence of (mostly asymptomatic) coeliac disease varies form 0.97 to 6.4%. Diabetes is usually diagnosed first. Screening in relatives may also be positive. Recurrent hypoglycaemia in diabetic subjects (indirectly) suggest the development of coeliac sprue. Thyroid disorders (thyroiditis and Graves' disease) are also usual in coeliac disease. A common etiopathogenic mechanism for the association CD/diabetes/thyroid disorders, with gluten as the driving antigen, was postulated. Thus, screening program for coeliac disease are recommended in individuals with type 1A diabetes and/or auto-immune thyroid conditions, as well as in their first-degree relatives.

Acta Gastroenterol Belg. 2003 Jul-Sep;66(3):237-40

Prevalence and early diagnosis of coeliac disease in autoimmune thyroid disorders.

Cuoco L, … and Gasbarrini G.

BACKGROUND AND AIMS: …….. METHODS: Total serum IgA were measured in all subjects to exclude selective IgA deficiency; then we measured anti-gliadin antibodies and anti-endomysial antibodies. In patients with anti-gliadin/anti-endomysial antibody positivity and/or with haematinic and laboratory signs of malabsorption we carried out gastrointestinal endoscopy with duodenal histological examination. RESULTS: Among the 92 patients with autoimmune thyroid disease, **4 (4.3%)** showed anti-gliadin and anti-endomysial positivity and **had coeliac disease**; among the 90 patients with non autoimmune thyroid diseases, 1 (1.1%) had coeliac disease; finally, **among the blood donors, 1 subject (0.4%)** was anti-gliadin-anti-endomysium antibody positive and had coeliac disease. ….. CONCLUSIONS: …….. We suggest a serological screening for coeliac disease in all patients with autoimmune thyroid disease measuring anti-endomysial antibodies, considering that early detection and treatment of coeliac disea

Ital J Gastroenterol Hepatol. 1999 May;31(4):288-9.

Clinical queries

1) What is the clinical impact of the diseases?

2) In cost-effective terms, which single component of the syndrome should be screened?

3) What should be the initial evaluation in order to exclude or confirm the syndrome?

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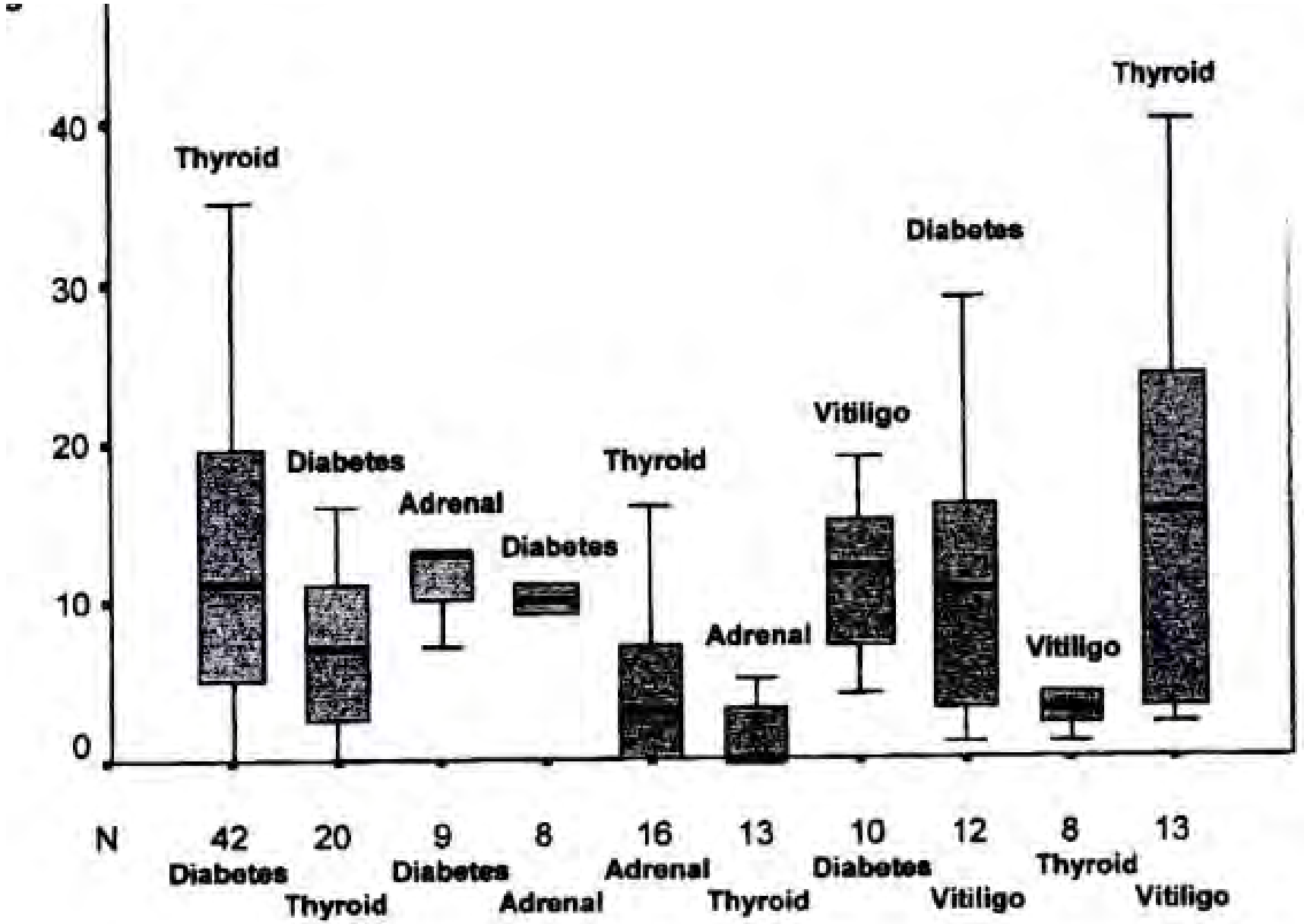


Dittmar M and Kahaly GJ, JCEM: 2003, 88(7):2983-2992

Symptoms and signs of alarm in patient at risk of APS

- Addison: hypoglycemia (especially if on insulin therapy), fatigue and hyperpigmentation
- Diabetes: polyuria, polydipsia, nausea and vomiting with ketoacidosis
- Hypothyroidism: easy faticability, coldness, weight gain, constipation
- Hyperthyroidism: nervousness, palpitation weight loss, intolerance to heat, diarrhea, fatigability
- Pernicious anemia: coordination difficulties
- Celiac disease: anemia, adbominal pain, diarrhea

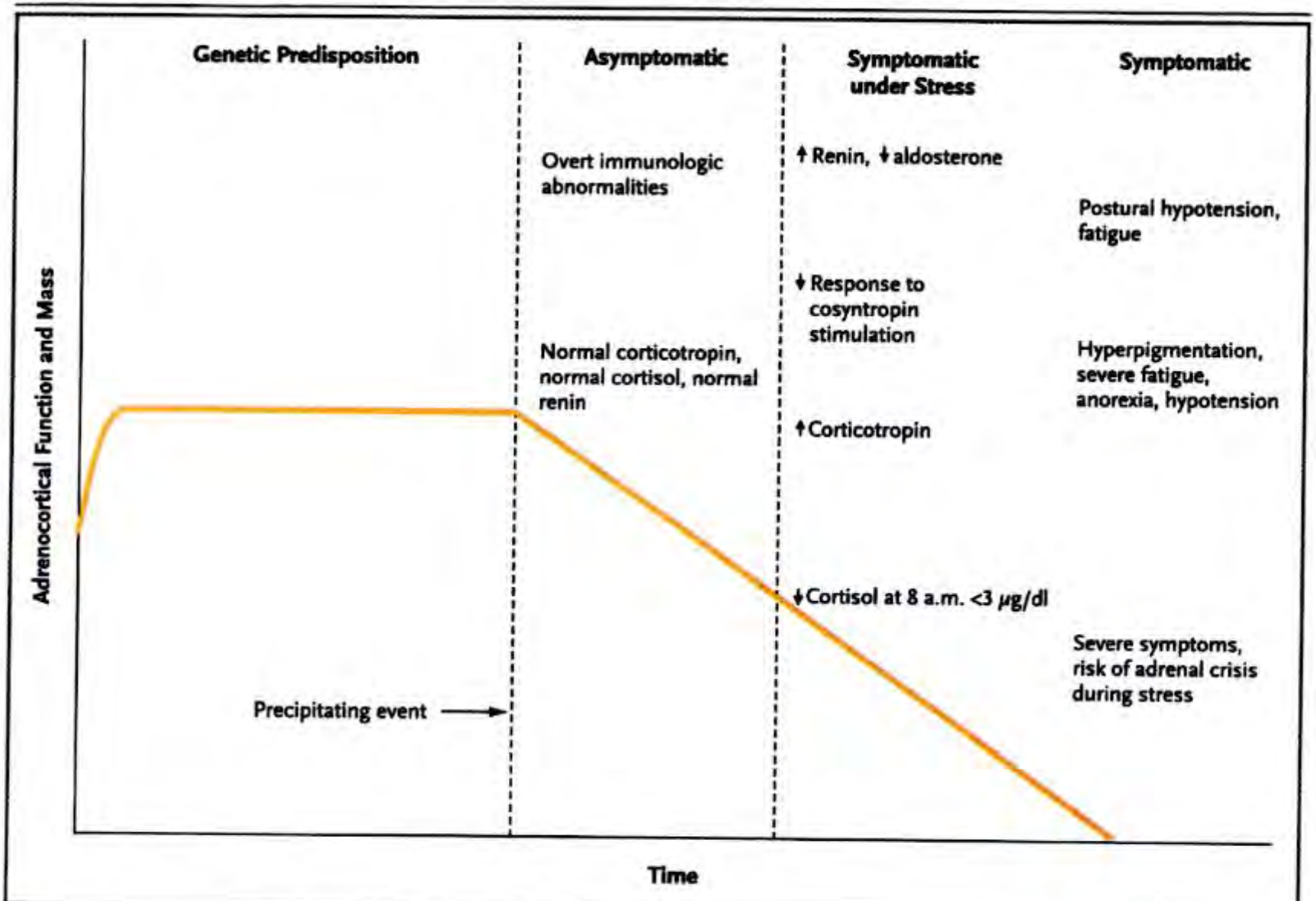
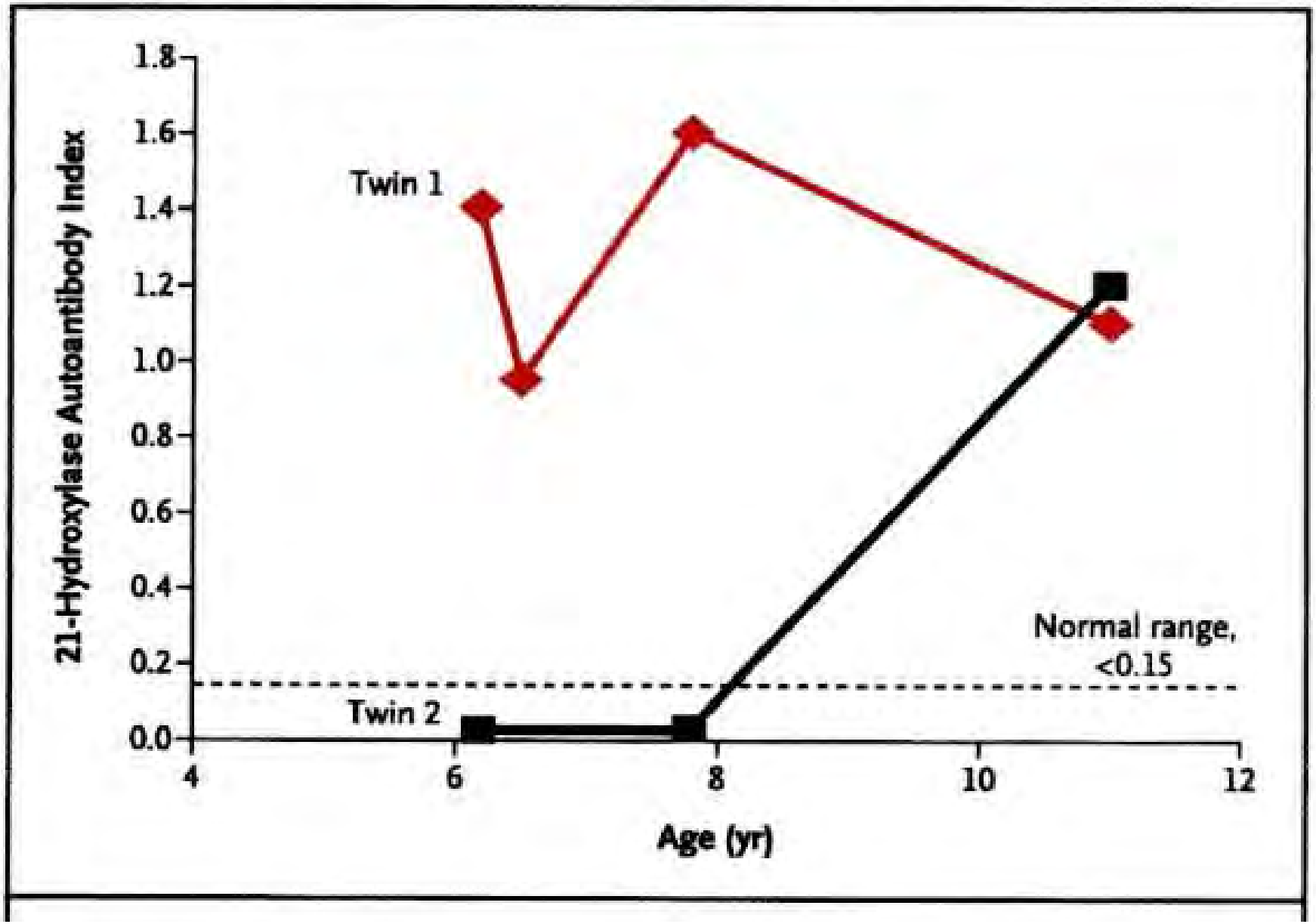


Figure 3. **Stages in the Development of Addison's Disease.**

Eisenbarth G and Gottlieb P. N Engl J Med 2004;350:2068-2079



Eisenbarth G and Gottlieb P. N Engl J Med 2004;350:2068-2079

AAD prediction score

Predictor variable		β
Age	< 16	0.38
	> 16	0
Gender	Male	1.21
	Female	0
Adrenal Function	Impaired (stages 1-3)	1.82
	Normal (stage 0)	0
Antibody titers	High	1.20
	Low-medium	0
Coesisting disease	Clinical or potential APS type 1	1.66
	Other condition	0
Baseline survival function at 5 yr, s(t)		0.9712

Coco G at all, JCEM 2006

Conclusions

Clinical query

Which single major component needs screening for the syndrome in cost-effective terms?

APS1: **none except hypoparathyroidism unless…**

APS2: **all principal endocrine disorders except thyroiditis unless …….**

Clinical query

Which single minor component needs screening for the syndrome in cost-effective terms?

APS1: **none except autoimmune gonadal failure unless…**

APS2: **none except autoimmune gonadal failure and myastenia gravis unless…**

Partial screening for thyroiditis seems proper due to high prevalence of the disease

Clinical query

Which non endocrine disease should be screened in autoimmune endocrine disease?

Celiac disease …..

and vitiligo

When antibodies toward a second and/or third organ target are present, patient with monoglandular disease should be screened yearly

Betterle et all, End Rev, 2002
Eisenbarth G and Gottlieb P. N Engl J Med 2004

Progressive Metabolic Abnormalities
APS type 2

- Elevated PRA is the first sign of adrenal damage
  (Betterle et all, End Rev, 2002)

- Loss of the first-phase insulin secretion in an intravenous glucose-tolerance test and reduction of plasma level of C-peptide
  (Chase et all, J Pediatr 2001)

- Elevation of TSH
  (50% of TPOAb + develops hypothyroidism whithin 10 yrs)
  (Eisenbarth and Gottlieb NEJM 2004)


Thank you

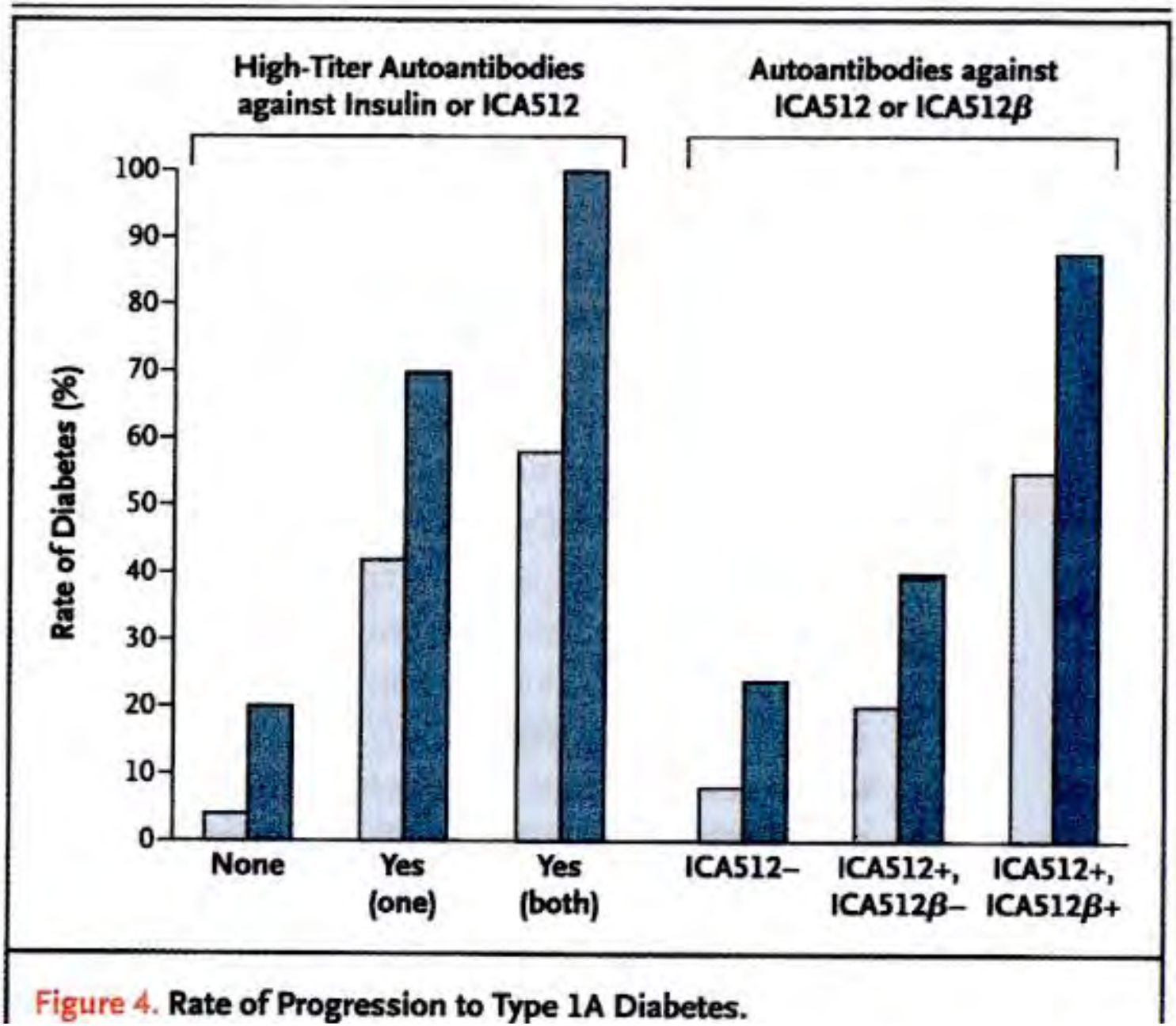


Figure 4. Rate of Progression to Type 1A Diabetes.

Eisenbarth G and Gottlieb P. N Engl J Med 2004;350:2068-2079

The 2006 recommendations on Thyroid & Pregnancy: focus on autoimmune thyroid disorders

Daniel Glinoer (Univ. of Brussels)

Update in Clinical Endocrinology

(Verona ; October 2006)

International Task Force under the auspices of the American Endocrine Society Recommendations « 2006 »

- Leslie De Groot (Chair) (USA – Brown Providence)
- Alex Stagnaro-Green (USA – New Jersey)
- Susan Mandel (USA – U. Penn) (ATA)
- Rhoda Cobin (USA – Mount Sinai NY) (AACE)
- Maureen Malee (Ob-Gyn) (USA – Chicago)
- Sarah Kilpatrick (Ob-Gyn) (USA – Chicago) (ACOG)
- Lynn Barbour (USA – Denver)
- Marcos Abalovich (Argentina – Buenos Aires) (LATS)
- Nobuyuki Amino (Japan – Kobe) (AOTA)
- Daniel Glinoer (Belgium – Brussels) (ETA)

Consensus Guidelines on THYROID & PREGNANCY (the 10 topics examined)

- Maternal hypothyroidism
- Fetal aspects << mat HO
- Maternal hyperthyroidism
- Fetal aspects << mat HR
- Gestational (non AI) hyperthyroidism
- Iodine nutrition
- Infertility & Miscarriage
- Postpartum thyroiditis
- Nodules and Cancer
- Screening for thyroid disorders

Consensus Guidelines on THYROID & PREGNANCY

- **Maternal hypothyroidism (2.5-3 %)**
- **Fetal aspects << mat HO**
- **Maternal hyperthyroidism (0.2 %)**
- **Fetal aspects << mat HR**
- **Gestational (non AI) hyperthyroidism (0.2 %)**

- **Iodine nutrition (> 1 billion with IDD)**
- **Infertility & Miscarriage**
- **Postpartum thyroiditis (50 % of Abs +)**
- **Nodules and Cancer**
- **Screening for thyroid disorders**

A few notions about the methodology employed …

- **Eight sections, each containing background info, available evidence from literature, recommendations with grading, remarks and bibliography**

- **Citation of each bibliographic reference on which the recommendations are based (with a summary of pertinent data)**

- **Overview of recommendations: 35 recommendations**

- **Grading systems : USPSTF and the « Montori Grade » system**

Hypothyroidism and pregnancy: maternal and fetal aspects

- Overt, known and already treated before pregnancy
- Overt, diagnosed during pregnancy
- Subclinical hypothyroidism
- Positive auto-antibodies with normal thyroid function
- Isolated hypothyroxinemia
- Fetal aspects related to maternal hypothyroidism

MATERNAL HYPOTHYROIDISM

- **1.1. Both maternal and fetal hypothyroidism are known to have serious adverse effects on the fetus.**

  →Therefore maternal hypothyroidism should be avoided.
  →Targeted case finding is recommended at the first prenatal visit or at diagnosis of pregnancy.

  (USPSTF: A; fair – GRADE: 1|⊕⊕⊕◯)

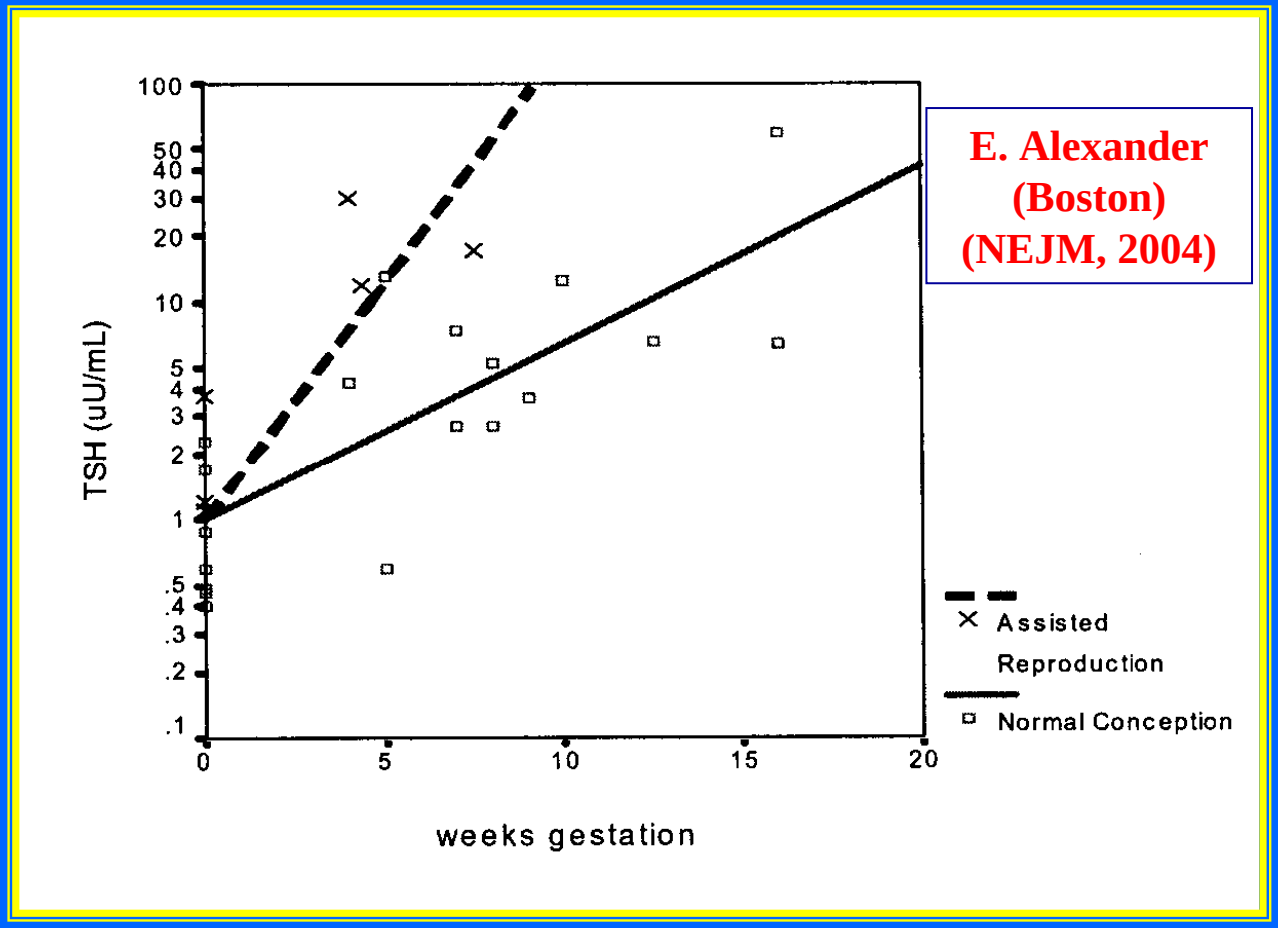
- **1.2. For hypothyroidism diagnosed before pregnancy:**

  We recommend adjustment of the preconception thyroxine dosage to reach a TSH level not higher than 2.5 mU/L prior to pregnancy.

  (USPSTF: B; poor – GRADE: 2|⊕◯◯◯)

MATERNAL HYPOTHYROIDISM

- **1.3. The thyroxine dose usually needs to be incremented by 4-8 weeks gestation, and may require a 30-50% increase in dosage.**



MATERNAL HYPOTHYROIDISM

❑ **1.4. If overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalized as rapidly as possible in view of the potential obstetrical complications and risks for the offspring associated with undisclosed prolonged hypothyroidism.**

Pregnancy co-morbidity associated with overt and subclinical hypothyroidism

- ❖ infertility & subfertility
- ❖ failure of IVF procedures
- ❖ spontaneous miscarriages
- ❖ gestational hypertension & preeclampsia
- ❖ premature delivery
- ❖ increased frequency of neonatal ICU admissions (respiratory distress syndrome, etc)

MATERNAL HYPOTHYROIDISM

❑ **1.4.** If overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalized as rapidly as possible in view of the potential obstetrical complications and risks for the offspring associated with undisclosed prolonged hypothyroidism.

Thyroxine dosage should be titrated to rapidly reach and thereafter maintain serum TSH concentrations of less than 2.5 mU/L in the 1st trimester (or <3 mU/L in the 2nd and 3rd trimester) or to trimester-specific normal TSH ranges.

Thyroid function tests should be remeasured within 30-40 days.

MATERNAL HYPOTHYROIDISM

***Note N° 1**: Hypothyroid pregnant women require larger l-T_4 replacement doses than non pregnant hypothyroid patients; the full replacement dose is 2-2.4 μg/Kg bw/day.*

***Note N° 2**: Trimester-specific ranges for serum TSH have not yet been universally established (or admitted).*

***Note N° 3**: There is a consensus **AGAINST** advising interruption of pregnancy, even if overt hypothyroidism is diagnosed late.*

***Note N° 4**: The magnitude of the increment in thyroxine dosage depends upon the cause of hypothyroidism: women without residual thyroid tissue usually require a greater and more rapid increment than those with Hashimoto's thyroiditis.*

False satisfaction and running behind the TSH

Hypothyroid pregnant women under l-T_4 (Nottingham City Hospital, UK)

	Trim 1	Trim 2	Trim 3
Daily dose	100 (25-275)	125 (25-300)	150 µg (25-325)
Median TSH	2.6	1.8	1.1 mU/L
TSH range	up to 34.4	up to 68.7	up to 95.7 mU/L

from Idris et al. Clin Endocrinol 2005
(retrospective study in 167 pregnancies)

Rule of thumb …

If serum TSH		*Increment in l-T_4*
5-10 mU/L	→	25-50 µg/day
10-20 mU/L	→	50-75 µg/day
> 20 mU/L	→	~ 100 µg/day

Hyperthyroidism due to Graves' disease and pregnancy: maternal and fetal aspects

- Differential diagnosis
- Medical treatment of GD
- Aims to reach
- Measurement of TRAb
- Fetal aspects related to maternal hyperthyroidism

MATERNAL HYPERTHYROIDISM

❑ **2.1. If a subnormal serum TSH concentration is detected, hyperthyroidism must be distinguished from both normal physiology and hyperemesis gravidarum because of the adverse effects of overt hyperthyroidism on mother and fetus.**

Differentiation of GD from gestational transient thyrotoxicosis 'GTT' is supported by presence of evidence of autoimmunity, a goiter, and presence of TSH-Rec antibodies.

(USPSTF: A; good – GRADE: 1|⊕⊕⊕⊕)

❑ **2.2. For overt hyperthyroidism due to GD, ATD therapy should be either initiated (for those with new diagnoses) or adjusted (for those with a prior history) to maintain maternal free T_4 levels in the trimester-specific normal pregnancy range (if available) or in the upper non pregnant reference range.**

(USPSTF: A; good – GRADE: 1|⊕⊕⊕⊕)

MATERNAL HYPERTHYROIDISM

- 2.3. Since available evidence suggests that MMI may be associated with congenital anomalies, PTU should be used as a first line drug (if available) especially during 1st trimester's organogenesis. MMI may be prescribed if PTU is not available, or if a patient cannot tolerate or has an adverse response to PTU.

- 2.4. Subtotal thyroidectomy may be indicated for maternal GD disease, if (1) there are severe adverse reactions to ATD; (2) persistently high ATD doses are required; or (3) a patient is non-adherent to ATD therapy and has uncontrolled hyperthyroidism. The optimal timing of surgery is in the second trimester.

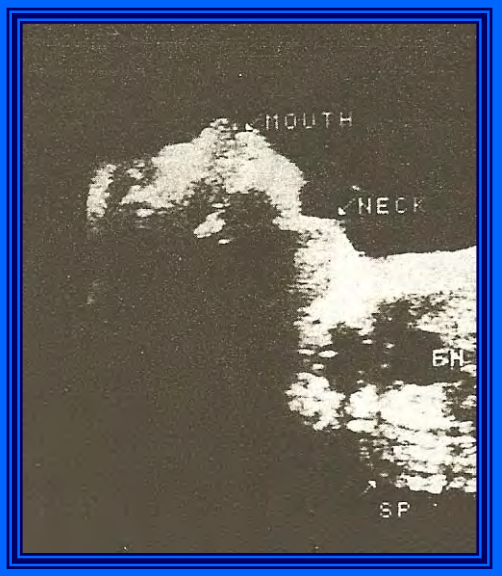
- 2.5. There is no evidence that treatment of subclinical hyperthyroidism improves pregnancy outcome, and treatment could potentially adversely affect fetal outcome.

Mother | **Placental barrier** | **Fetus**

Anti-TSH receptor antibodies (TRAb or TBII) with stimulating and/or blocking activity

Thionamide antithyroid drugs (PTU, MMI, CMI)

Hyperthyroidism ?



Hypothyroidism ?

MATERNAL HYPERTHYROIDISM: FETAL ASPECTS

- **2.2.1. TSH-Rec Abs freely cross the placenta and can stimulate the fetal thyroid.**

  → These antibodies should be measured before pregnancy or by the end of the 2nd trimester in mothers with current GD, or with a history of GD and treatment with I-131 or thyroidectomy, or with a previous neonate with GD.

  → Women who have a negative TRAb and do not require ATD have a very low risk of fetal or neonatal thyroid dysfunction.

  (USPSTF: B; fair – GRADE: 1|⊕⊕⊕⊕)

- **2.2.2. 131-I should not be given to a woman who is (or may be) pregnant.**

  → If inadvertently treated, the patient should be promptly informed of the radiation danger to the fetus, including thyroid destruction if treated after the 12th week of gestation.

  → There are no data for or against recommending termination of pregnancy after radioiodine exposure.

MATERNAL HYPERTHYROIDISM: FETAL ASPECTS

- **2.2.3. In women with elevated TRAb or in women treated with ATD, fetal ultrasound should be performed to look for evidence of fetal thyroid dysfunction that could include growth restriction, hydrops, presence of goiter, or cardiac failure.**

- **2.2.4. Umbilical blood sampling should be considered only if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical data and if the information gained would change the treatment.**

- **2.2.5. All newborns of mothers with GD should be evaluated by the medical care provider for thyroid dysfunction and treated if necessary.**

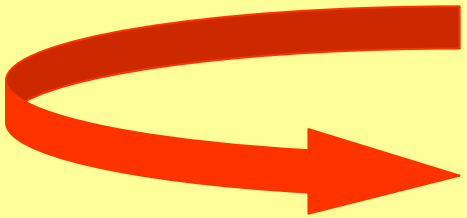
Fetal & neonatal thyroid dysfunction in newborns from mothers with GD

Adapted from Luton et al (JCEM , 2005)

72 mothers with present or past Graves' disease

- 31 mothers : no ATD and negative TRAb
  → **all newborns were normal**

- 41 mothers : with ATD and/or positive TRAb
  → **30/41 newborns : normal fetal US thyroid**
  normal TFTs (except for 1)
  → **11/41 newborns : fetal goiter at US examination**
  abnormal TFTs
  → **7 hypothyroid**
  → **4 hyperthyroid**



(hypo : low TRAb ; high ATD)
(hyper : high TRAb ; low ATD)

The issue of systematic screening

- Available literature on screening (Montori and his associates)
- Over 500 abstracts were screened
- 64 articles considered eligible for further evaluation
- 29 articles excluded (because lacking an intervention component)
- 35 articles potentially eligible, analyzed, and finally rejected because they did not meet the criteria

- **Conclusion: no study satisfied the criteria for forming the basis of a recommendation for/against screening.**

→ **partially satisfactory « solution » : case finding (targeted or agressive)**

Although the benefits of universal screening for hypothyroidism may not be justified by current evidence, we recommend case finding among the following groups of women at high risk for thyroid dysfunction (USPTF: B; fair – GRADE: 1|⊕⊕◯◯)

1. Women with a history of hyperthyroid or hypothyroid disease, postpartum thyroiditis, or thyroid lobectomy
2. Women with a family history of thyroid disease
3. Women with a goiter
4. Women with thyroid antibodies (when known)
5. Women with symptoms or clinical signs suggestive of thyroid underfunction or overfunction (including anemia, elevated cholesterol, and hyponatremia)
6. Women with type I diabetes
7. Women with other autoimmune disorders
8. Women with infertility should have screening with TSH as part of their infertility work-up
9. Women with prior therapeutic head or neck irradiation
10. Women with a prior history of preterm delivery

Is thyroxine the answer ?

(Negro et al; JCEM 91:2587, 2006)

N =	**57**	**58**	**869**
TPO-Ab	**+**	**+**	**-**
L-T4	**+**	**-**	**-**
TSH (onset)	**1.6**	**1.7**	**1.1**
TSH (deliv)	**1.9**	**3.5**	**2.1**
FT4 (onset)	**1.49**	**1.48**	**1.51**
FT4 (deliv)	**1.44**	**1.03**	**1.45**
MC (%)	**2.5**	**12.8**	**2.4**
PD (%)	**7.0**	**22.4**	**7.0**

A few personal conclusions

1. **Altogether, this effort represented a tremendous challenge (much more difficult than anticipated)**

2. **Different approach for some relevant items between endocrinologists and ob-gyn, but also a success to be able to work together**

3. **Diplomatic search for compromise in order to reach consensus views**

4. **End result: a 86-page document (single spaced !!) including 35 recommendations**

5. **Few prospective randomized trials in the field → expert opinions needed**

6. **Additional data appearing during the work of the task force (Alexander ; Negro)**

7. **Will it be endorsed and what will the final outcome be?**

EVIDENCE-BASED RECOMMENDATIONS

USPSTF = U.S. Preventive Services Task Force*

(*Guide to Clinical Preventive Services, Third Edition: Periodic Updates, 2002-2003)

A : strongly recommend … (< based on good evidence)
B : recommend … (< fair evidence)
C : makes no recommendation for or against or recommends (< expert opinion) … (< fair evidence but balance between benefits and harms is too close)
D : recommend against … (< based on good evidence)
I : evidence is insufficient to recommend for or against … (< lack of evidence)

Quality of overall evidence

Good: → consistent results from well-designed studies
Fair: → evidence sufficient to determine effects on health outcome but strength limited by number, quality or consistency of data
Poor: → evidence insufficient to assess the effects on health outcomes

EVIDENCE-BASED RECOMMENDATIONS

GRADE system (Victor Montori; Mayo Clinic College of Medicine)

In the GRADE system, the strength of a recommendation is indicated by the number

1 : strong recommendation, associated with the phrase "we recommend …"

2 : weak recommendation, associated with the phrase "we suggest …"

High quality evidence: "⊕⊕⊕⊕" (further research is very unlikely to change our confidence in the estimate of effect) → RCT

Moderate quality evidence: "⊕⊕⊕◯" (further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) → non RCT

Low quality evidence: "⊕⊕◯◯" (further research is unlikely to have an important impact on our confidence ….) → observational studies

Poor quality evidence: "⊕◯◯◯" (any estimate of effect is very uncertain)

Lack of control of hyperthyroidism is associated with adverse pregnancy outcome

	poor control	less than adequate control	adequate control	
• Preeclampsia	14-22%	--	7%	Davis (89)
• Congestive heart failure	60%	--	3%	Millar (94)
• Thyroid storm	21%	--	2%	Mestman (04)
• Preterm delivery	88%	25%	8%	Millar (94)
• LBW (< 2500 gr)	23%	--	10%	Phoojaroencha-nachai (01)

Fetal thyroid dysfunction induced by maternal TRAb (TSH-Rec stimulating antibodies)

Adapted from Mitsuda (1992)

Maternal TRAb (at delivery)	Neonatal thyroid dysfunction
< 130 % of normal	**11 %**
> 130 % of normal	**67 %**
> 150 % of normal	**83 %**

(< 115 % = upper normal level)