Classificazione ed Epidemiologia degli Iposurrenalismi

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(Dichiaro di non avere conflitto di Interessi)

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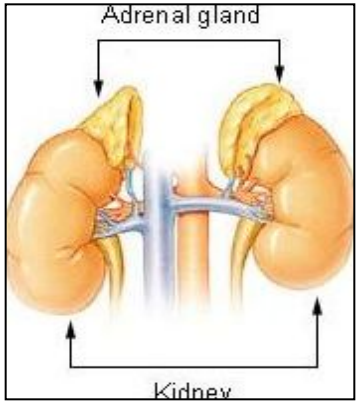
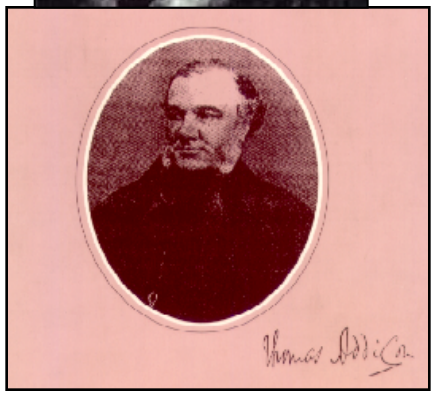
AZIENDA OSPEDALIERA UNIVERSITA' PADOVA

LA MALATTIA DI ADDISON

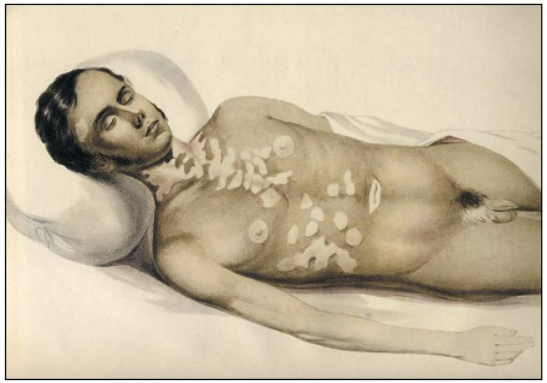
Bari,
7-10 novembre 2013

1563
Bartolomeo Eustachio
Anatomico a Padova
in the Opuscola Anatomica (Venice 1563 described the existence of the adrenals as "de glandulis quae renibus incumbent"





1855
Thomas Addison
Guy's Hospital di Londra,
descrive una malattia che colpisce
i surreni
e che porta a morte i pazienti
con una serie di disturbi:
estrema stanchezza
e colorito bruno della cute.



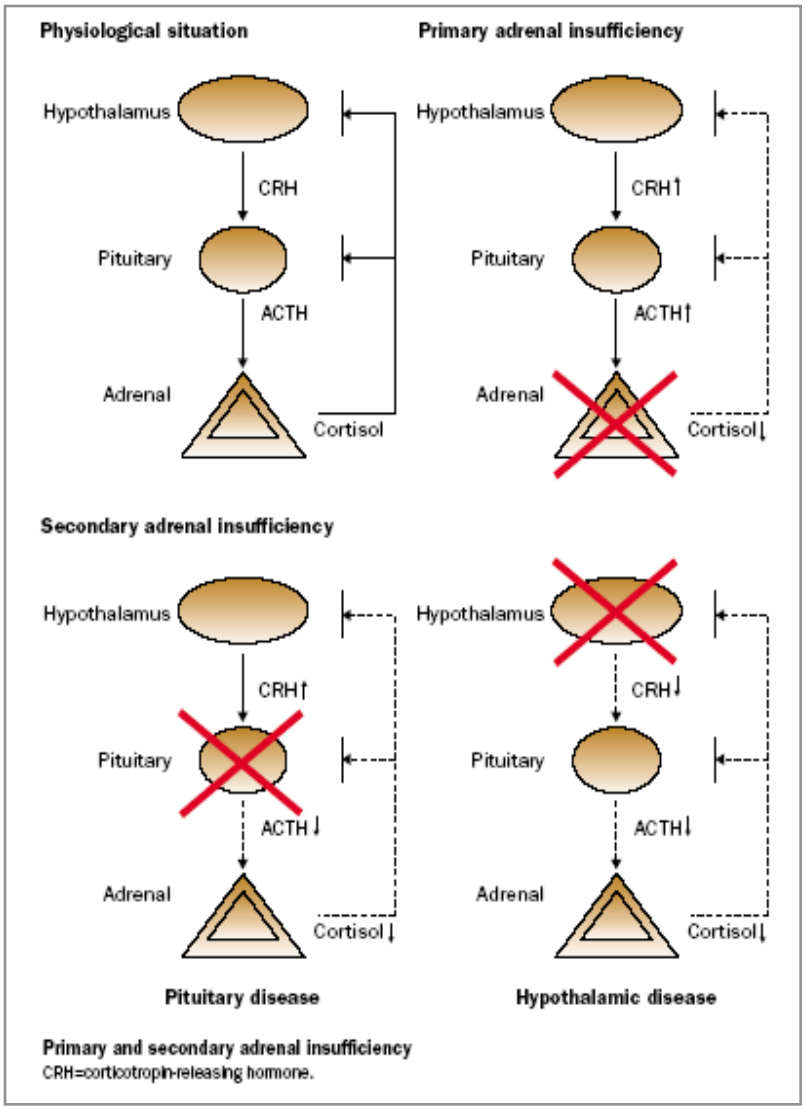
1856 Trousseau
l'insufficienza surrenalica fu chiamata **"malattia di Addison"**

descrisse 11 pazienti in cui l'autopsia rilevò a livello del surrene:
- 6 casi tubercolosi
- 3 casi tumori
- 1 caso emorragia
- 1 caso atrofia idiopatica

Questo probabilmente è la prima descrizione di una forma autoimmune.

Three types of adrenocortical insufficiencies

Bari,
7-10 novembre 2013



W. Arlt and B. Allolio The Lancet 361:1881-1893;2003

Prevalence of Addison's disease in the World

(x million of inhabitants)

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40	Cases in England (1968)
60	Cases in Denmark (1974)
93	Cases in England (1997)
110	Cases in England (1994)
117	Cases in Italy (2002)
144	Cases in Norway (2007)

In the years 1968-2004 the frequency of AD in Europe increased from 40-144 cases

4	cases in New Zealand
5	cases in Japan
50	cases in U.S.A.

	In the past	In recent years
TUBERCULOSIS	60-80%	10-15%
AUTOIMMUNITY	10-20%	75-80%
OTHERS	5%	5%

CLINICAL STUDY

European Journal of Endocrinology (2013) **169** 773–784

Addison's disease: a survey on 633 patients in Padova

Corrado Betterle, Riccardo Scarpa, Silvia Garelli, Luca Morlin, Francesca Lazzarotto, Fabio Presotto[1], Graziella Coco[†], Stefano Masiero, Anna Parolo, Maria Paola Albergoni[2], Roberta Favero[2], Susi Barollo, Monica Salvà, Daniela Basso[3], Shu Chen[4], Bernard Rees Smith[4], Jadwiga Furmaniak[4] and Franco Mantero

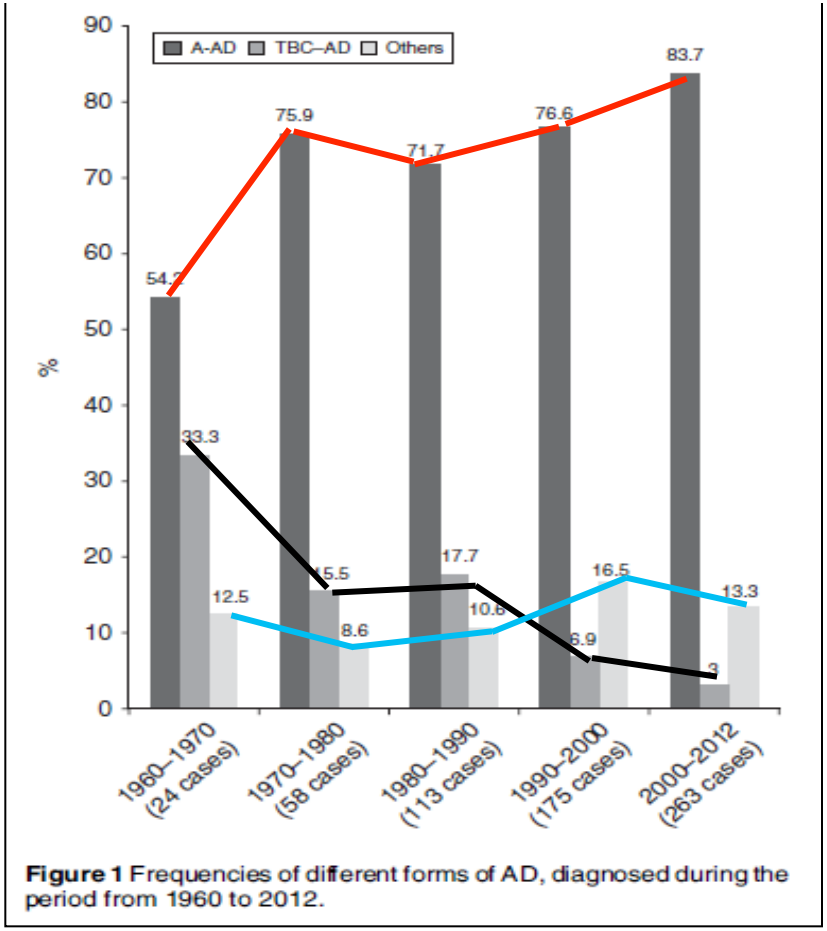

Figure 1 Frequencies of different forms of AD, diagnosed during the period from 1960 to 2012.

Epidemiologia del Morbo di Addison

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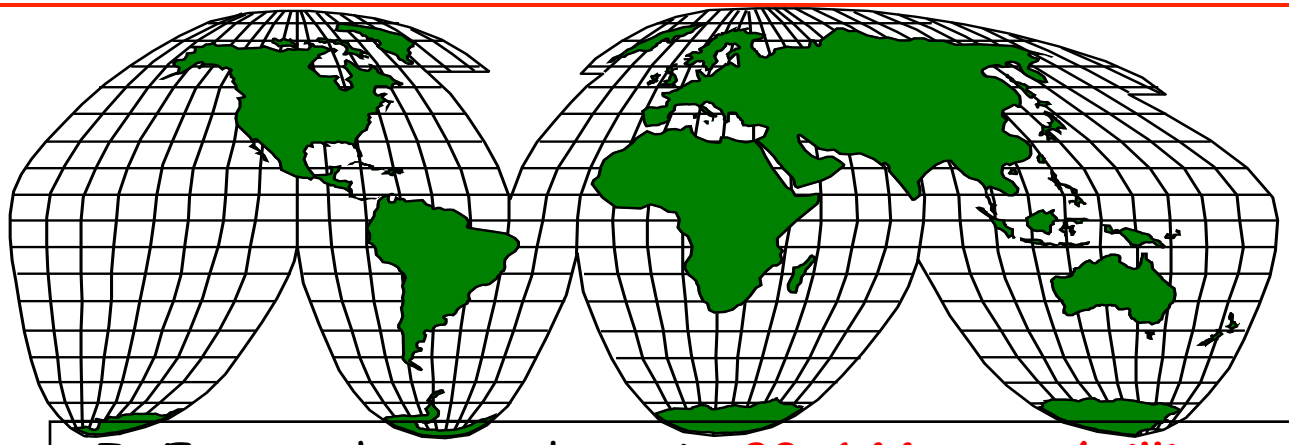

In **Europe** the prevalence is: **90-144 cases/million**
(Inhabitants 731 Millions)

70-100.000 patients with Addison's Disease

Incidence:4-6 new cases/million /year

3655 new cases/year=10 new cases/day

In **Italy** the prevalence is: **117 cases/million**
(Inhabitants 60 Millions)

7.000 patients with Addison's disease

300 new cases/year =about 1 new case/day

EurAdrenal

SEVENTH FRAMEWORK PROGRAMME

CLINICAL STUDY

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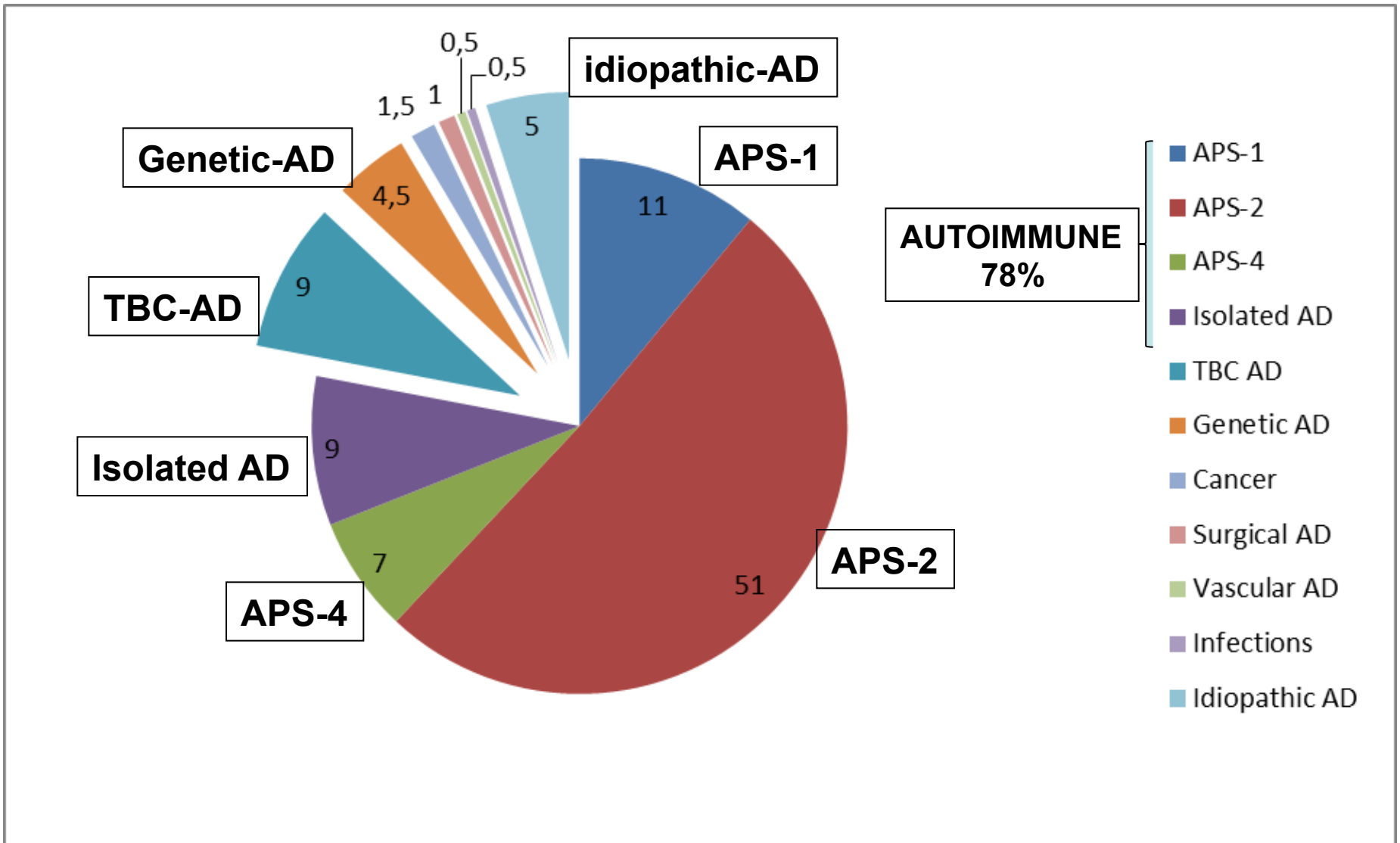

Age at onset of Different aethiological Forms of Addison's disease

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APS1

Non -APS1

TBC-AD

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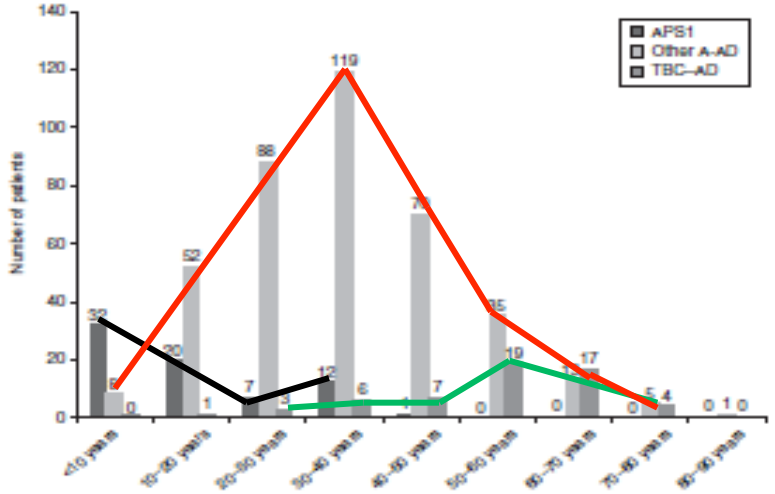

Figure 2 Age at the onset of AD in patients with APS1, other forms of autoimmune AD (APS2, APS4, and isolated A-AD) and with tuberculosis disease (TBC–AD).

GENETIC FORMS IN PADUA SURVEY

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Genetic Forms 29/633 (4,6%)

Patients with genetic forms of AD

Twenty-four of 29 (all males) had adrenoleukodystrophy with a mean age at onset of 18 years (range 1–63), two had 21-hydroxylase deficiency, one had X-linked congenital adrenal hypoplasia with mutation of *DAX1* (*NROB1*) (dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1), one had POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein skin abnormalities), and one had ACTH receptor mutation. ACA and 21-OHAbs were negative in 22 patients tested.

- 29 cases Adrenoleukodystrophy
- 2 cases 21-OH deficiency
- 1 case X linked
- 1 case POEMS
- 1 case ACTH receptor mutation

Bari,
7-10 novembre 2013

J Clin Endocrinol Metab, June 2005, 90(6):3243–3250

Primary Adrenal Insufficiency in Children: Twenty Years Experience at the Sainte-Justine

Rebecca Perry, Oufae Kecha, Jean Paquette, Celine Huot, Guy Van Vliet, and Cheri Deal

TABLE 1. Etiologies of PAI

Etiology	Females (n = 55)	Males (n = 48)	% of total (n = 103)	Age at diagnosis of PAI
21OH CAH				
Classic	30	29	57.3	
SW form	27	26	51.5	16 (1–2281) d[a]
SV form	3	3	5.8	5.8 (3.7–7) yr
Nonclassic	11	2	12.6	7.4 (5–10.3) yr
3-β-hydroxysteroid dehydrogenase deficiency CAH	1	1	1.9	17.5 (14–21) d
Autoimmune				
APECED	3	2	4.9	10.7 (5.4–13.6) yr
Non-APECED	5	3	7.8	14.6 (7.8–16.3) yr
Adrenoleukodystrophy	0	4	3.9	10.5 (4.3–14.3) yr
Syndromes				
Wolman disease	1	2	2.9	26 (25–49) d[b]
Triple A	0	1	1.0	10.3 yr
Zellweger disease	0	1	1.0	8.2 yr
X-linked AHC	0	1	1.0	4.6 yr
Unexplained isolated glucocorticoid deficiency	2	1	2.9	42 (6–122) d
Unexplained glucocorticoid and mineralocorticoid deficiencies	2	1	2.9	2.3 (1.2–4.3) yr

72%

12,7%

10%

[a] If the boy with a late diagnosis made after identification of his virilized infant sister is excluded, the median is unchanged, but the range becomes 1–1125 d.

[b] Age at presentation, not diagnosis (which was made postmortem; see *Results*).

PRIMARY ADRENOCORTICAL INSUFFICIENCY in Adult Population

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	AETHIOLOGY	PREVALENCE
AUTOIMMUNE	**Unknown**	**75-80%**
TUBERCULOSIS	**Mycobacterium TBC**	**10-12%**
Other infections	Histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, North America blastomycosis, cryptococcosis, syphilis, HIV, CMV	1%
Cancer or Metastatic disease	Adenocarcinoma, lymphomas, plasmocytomas, metastasis of ovary, colon, kidney, melanoma, brest cancer	1-2%
Infiltrative disorders	Amyloidosis, haemochromatosis, histiocytosis	1%
Congenital and Genetics	**agenesia, adrenoleukodystrophy, enzymatic defects, ACTH-receptor mutations, rare diseases**	**4-5%**
Vascular	Thrombosis, haemorrhage, drugs, traumas	1%
Drugs	ketoconazole, mitotane, metopyrone, aminoglutethimide, trilostane, etomidate, rifampin, cyproterone acetate, fenitoin sodium, barbiturate	1%
Surgery	for Cushing sindrome, for cancer	1%

The patway of adrenal cortex hormones

MINERALOCORTICOIDS | GLUCOCORTICOIDS | ANDROGENS

Cholesterol

Side chain cleavage

17α-hydroxylase

17-20 lyase

Pregnenolone → 17-OH Pregnenolone → DHEA

3β-OHDS

Progesterone → 17-OH Progesterone → Androstenedione

21-hydroxylase

11-Deoxycorticosterone

11-Deoxycortisol

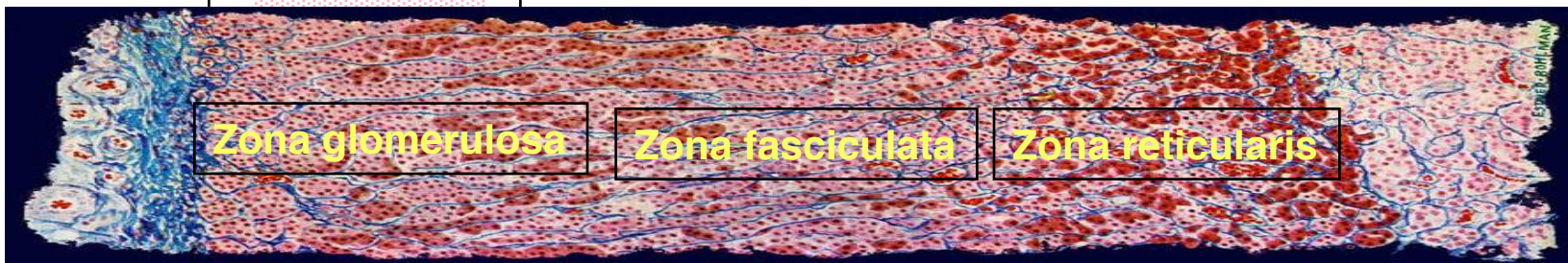
Testosterone

11β-hydroxylase

Corticosterone

Cortisol

Aldosterone



CLINICAL MANIFESTATIONS OF ADDISON'S DISEASE

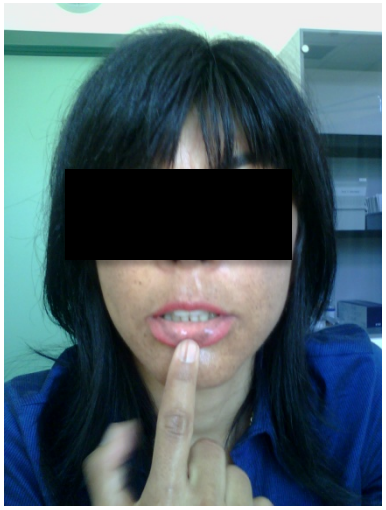
Symptoms	Incidence %
Weakness and fatigue	100
Anorexia	100
Nausea, vomiting and diarrhea	50
Salt craving	20
Muscle, joint and abdominal pain	10
Postural dizziness	10
Depression, psycosis	10

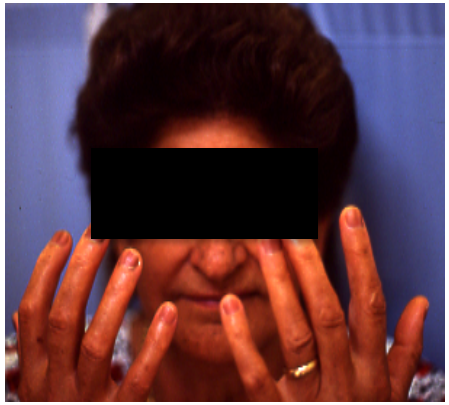
Signs	Incidence %
Weight loss (deidratation, vomiting, anorexia)	100
Orthostatic hypotension	90
Hyperpigmentation (skin,mucosae)	90
Decreased of axillary and pubic hairs	20

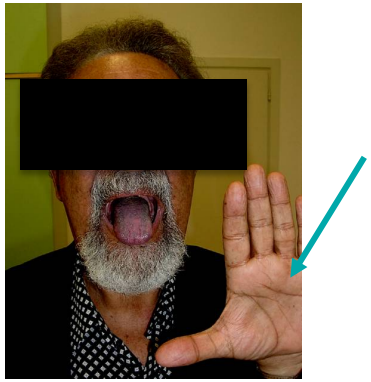
LABORATORY DIAGNOSIS OF ADDISON'S DISEASE

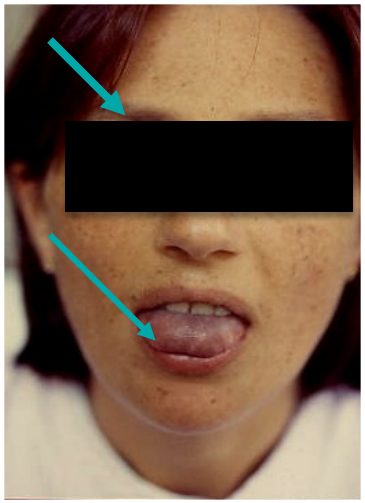
Natremia:	***low (<135mMol/L)***
Potassemia:	***increased (>4,5mMol/L)***
Chloremia	***low (<100 mMol/L)***
Plasm. Osmolarity	***low***
AST/ALT	***increased***
Calcemia:	***increased***
Glicaemia:	***low***
eosinophilia	
lymphocytosis	
anemia	
Cortisol:	***low***
ACTH:	***increased***
Aldosterone:	***low***
PRA:	***incraesed***
DEHAS:	***low***
TSH:	***increased***

CLINICAL MANIFESTATIONS OF ADDISON'S DISEASE









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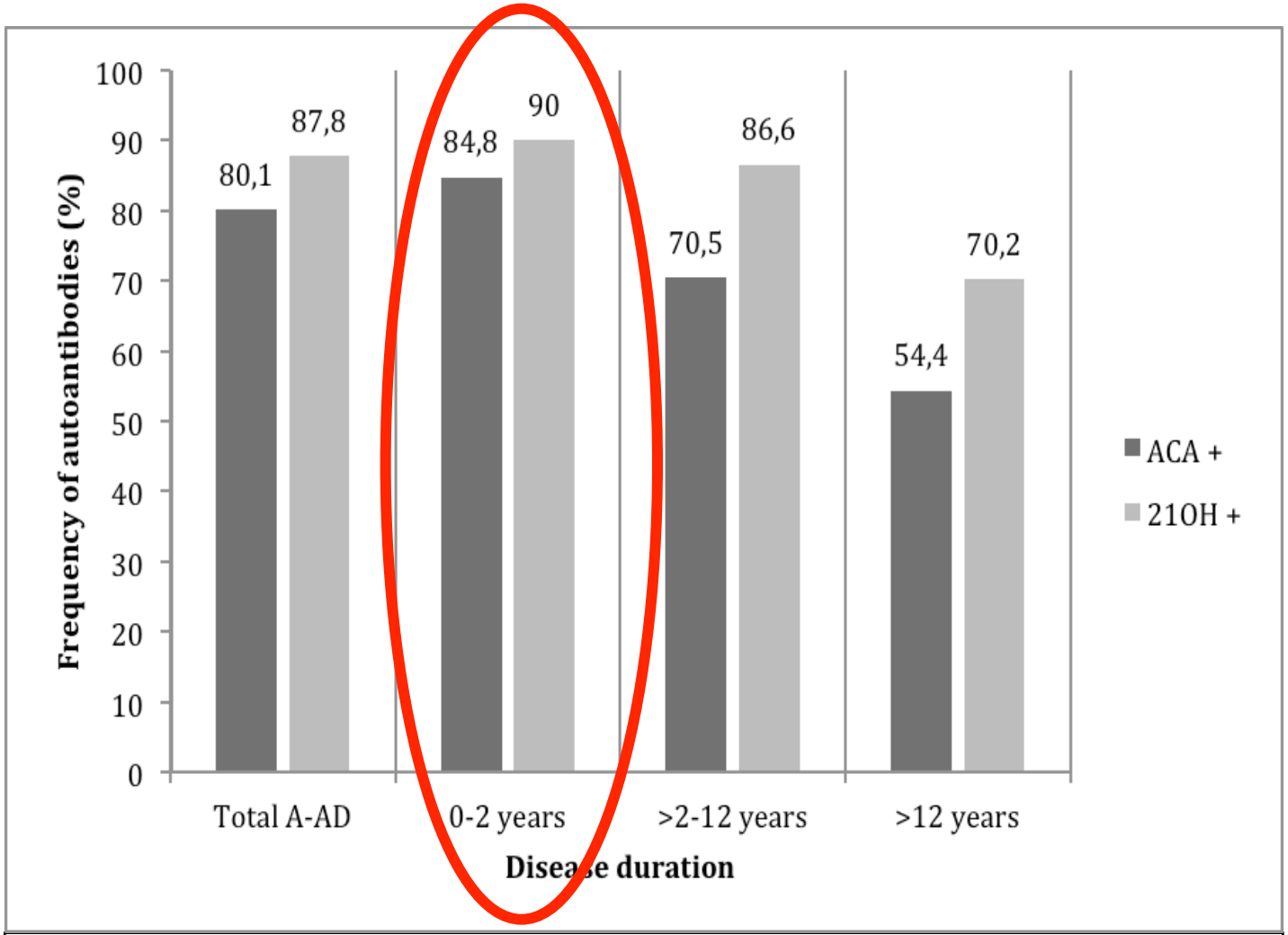

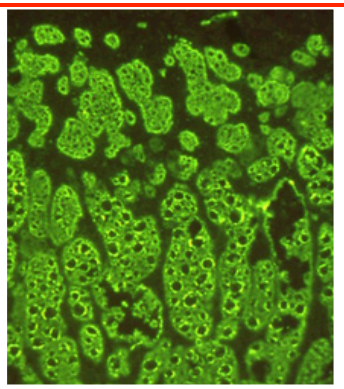

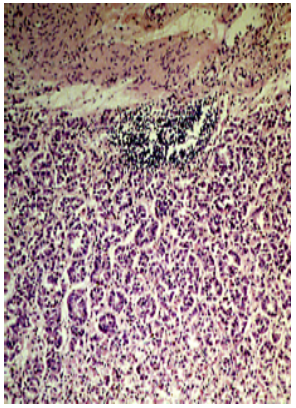

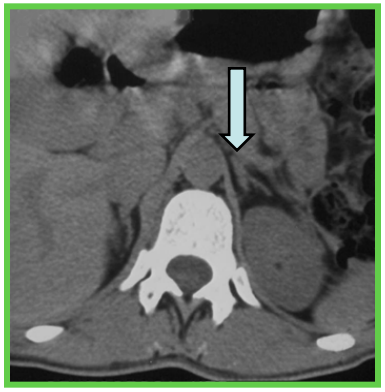

Adrenal cortex antibodies (ACA) and 21-OHAbs in A-AD

MORBO DI ADDISON AUTOIMMUNE: 4 DIFFERENT I PRESENTAZIONI CLINICHE

Bari,
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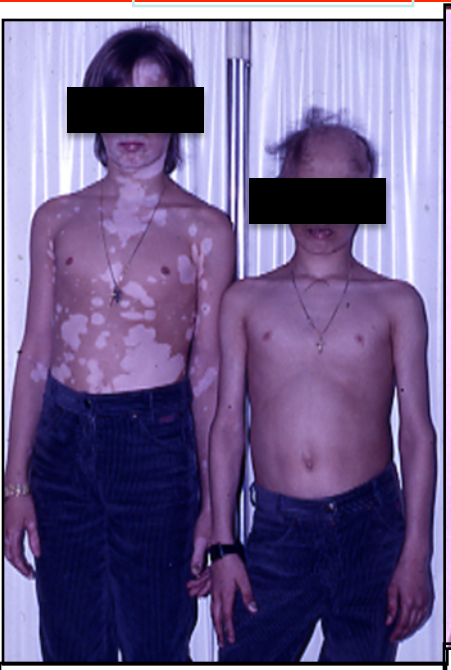
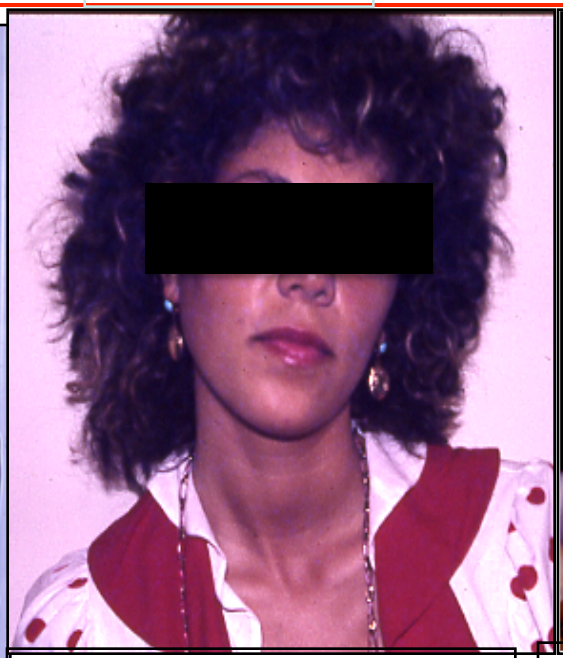
APS-1 (11%)



Morbo di Addison
+
Candidiasi Cronica
e/o
Ipoparatiroidismo

Bambini/Adulti 2/1
Età media 14 anni
F/M=1
Mutazioni GENE AIRE

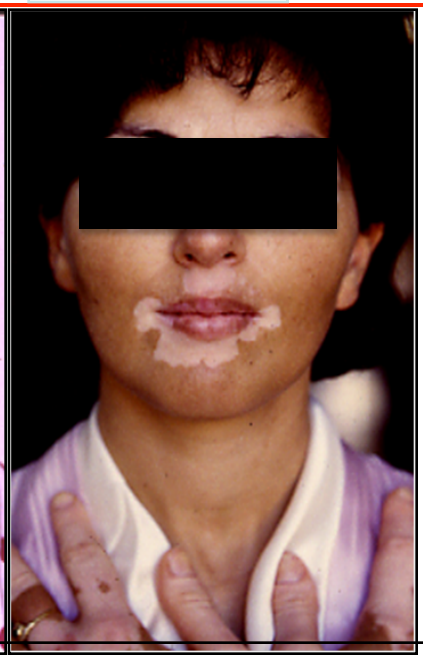
APS-2 (51%)



Morbo di Addison
+
Malattie tiroidee
e/o
Diabete Mellito Tipo 1

Adulti/Bambini 16/1
Età media 35 anni
F/M=2/1
HLA-DR3 and/or DR4

APS-4 (7%)



Morbo di Addison
+
Altre malattie autoimmuni (vitiligo, alopecia, gastrite, celiachia)

Adulti/bambini 5/1
Età media 35 anni
F/M=1
HLA-DR3 and/or DR4

Isolato (9%)

Morbo di Addison

Senza altre malattie autoimmuni

Adulti/Bambini 4/1
Età media 35 anni
F/M=0.6
HLA-DR3 and/or DR4

TUBERCULOSIS ADDISON'S DISEASE
57/633 cases (9%)
Pathology, Imaging and Laboratory

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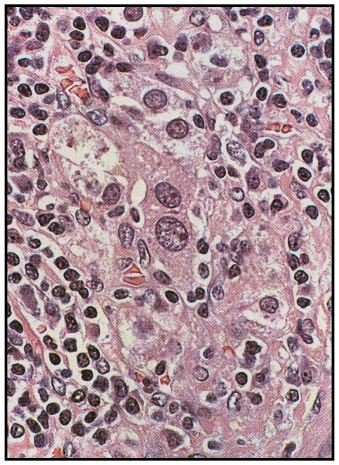
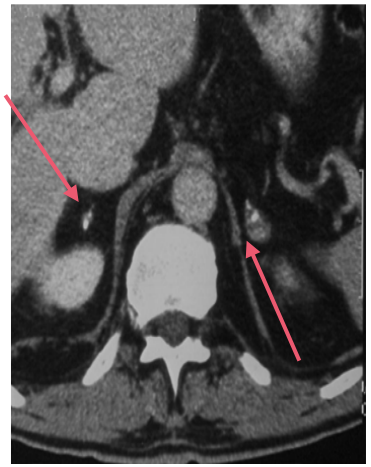
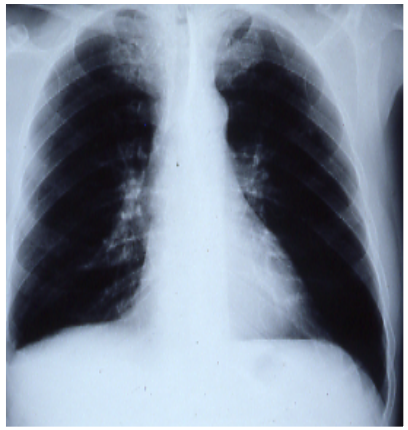
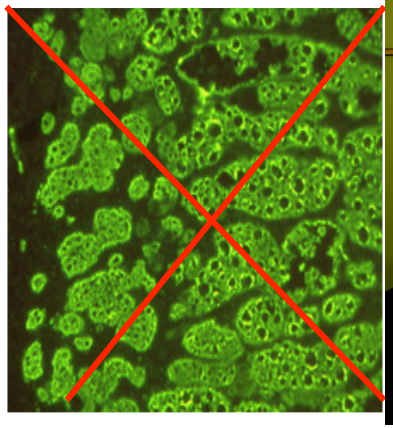
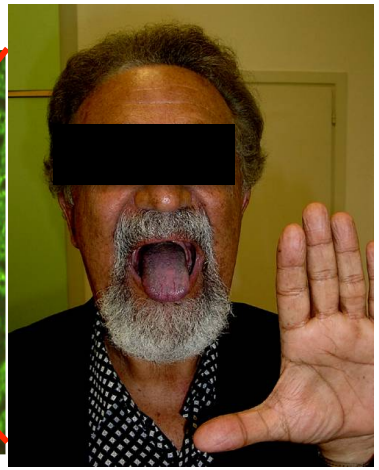


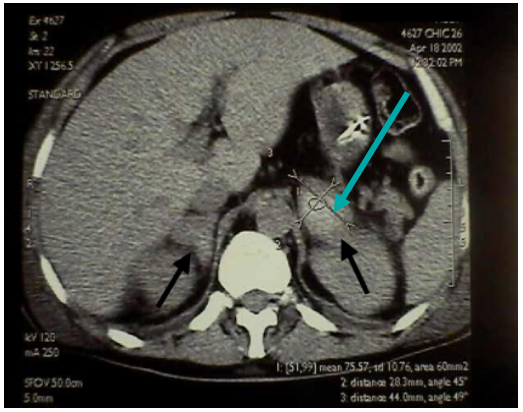








F/M 4/1
mean age 55



- **Adrenals Imaging:**

-87% revealed adrenal masses with or without calcifications
-13% showed normal adrenal glands.

ADDISON'S DISEASE and Adrenoleukodystrophy
24/633 cases (3,9%)

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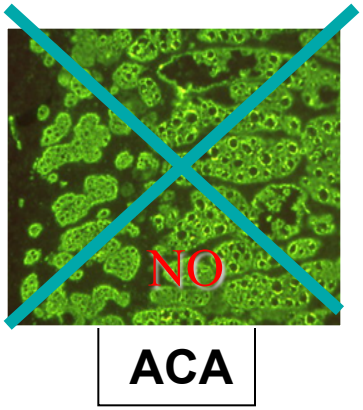
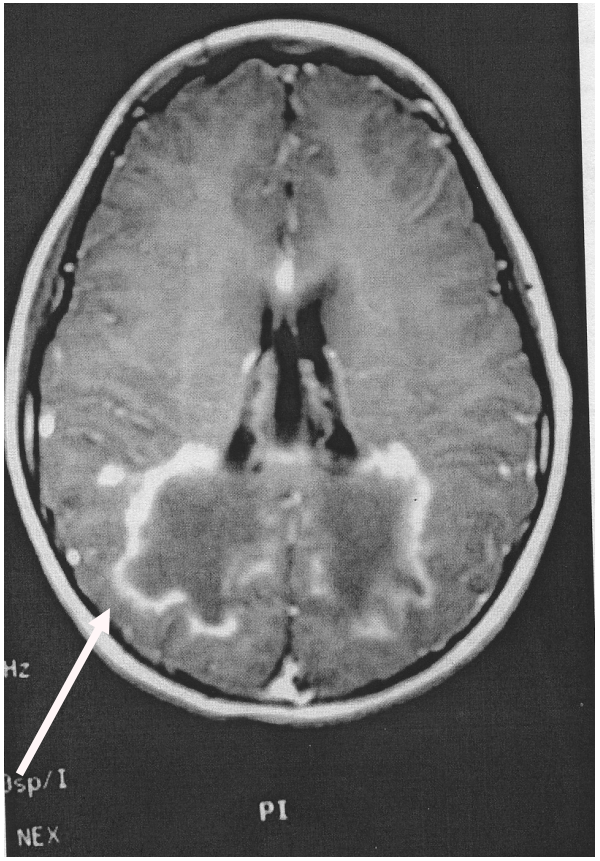


- All patients were males
- age at onset of AD 18 years
- VLCFA= were increased
- Adrenal imaging= were normal
- Brain imaging = symmetrical demyelinization

In 5 patients the AD was the first manifestation

Imaging



Etiological flowchart of Addison's disease in adults

Bari,
7-10 novembre 2013

ACTH ↑ CORTISOL ↓
Primary

ACA and/or 21-OHAbs

75% → **Positive** → **Autoimmune**

Adrenal imaging
Normal/atrophic
(not necessary)

Evaluation for other autoimmune diseases
(clinical and/or serological)

Candidiasis and/or Hypopara-thyroidism	TAD and/or Type 1DM	Presence of other autoimmune diseases	Absence of autoimmune diseases
APS 1	**APS 2**	**APS 4**	**Isolated**
AIRE GENE Mutations	HLA-DR		

25% → **Negative** → **Adrenal imaging**

Normal adrenal glands	Small hyperdense glands	Adrenal mass with or without calcifications	Atrophic or hyperplastic glands	Infarction or hemorrhage
VLCFA	**Adrenoleukodystrophy**	**Hemochromatosis**	**TBC**	**Neoplastic disease**	**Amyloidosis, Sarcoidosis, Histiocytosis, Fungal or viral Diseases**	**ACTH-test**	**ANA and/or APA**
Negative	**Positive**	**Adrenal biopsy?**	ACTH-R gene, SF-1, DAX-1, mitochondrial DNA deletions, enzyme defects	Positive	Negative
	Neurologic signs	Hemochromatosis	**TBC in other organs**	Neoplasia in other organs	Localization in other organs	Positive: Genetic forms; Negative: Idiopathic	SLE, APAS	Coagulation disorders, traumas, anti-cogulant therapy
	Chr. Xq28 mutations	HLA-DR						

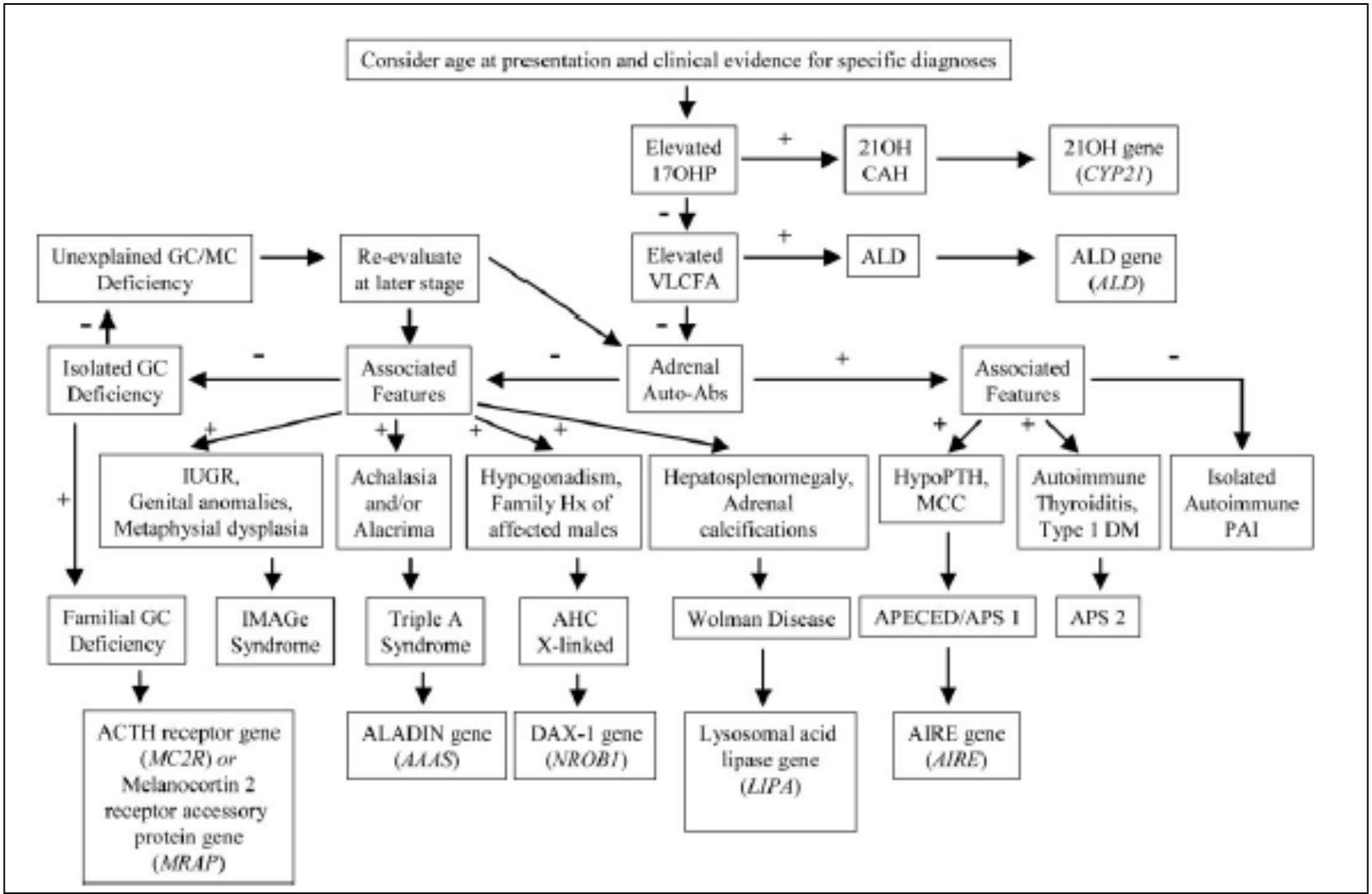
APAS = Anti-phospholipid syndrome; VLCFA = Very long chain fatty acids;
ACA = Adrenal-cortex autoantibodies; 21-OH Abs = 21-Hydroxylase autoantibodies
ANA = Anti-nuclear antibodies; APS = Autoimmune Polyendocrine Syndrome

J Clin Endocrinol Metab, June 2005, 90(6):3243–3250

Primary Adrenal Insufficiency in Children: Twenty Years Experience at the Sainte-Justine

Rebecca Perry, Oufae Kecha, Jean Paquette, Celine Huot, Guy Van Vliet, and Cheri Deal

Bari,
7-10 novembre 2013

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