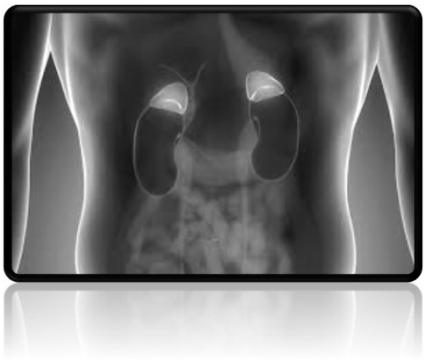
Lab Tests Related to Adrenal Cortex Insufficiency

M Reza Bakhtiari, DCLS, PhD



dr.bakhtiari.academy

1

Definition & Epidemiology

2

Hypoadrenalism

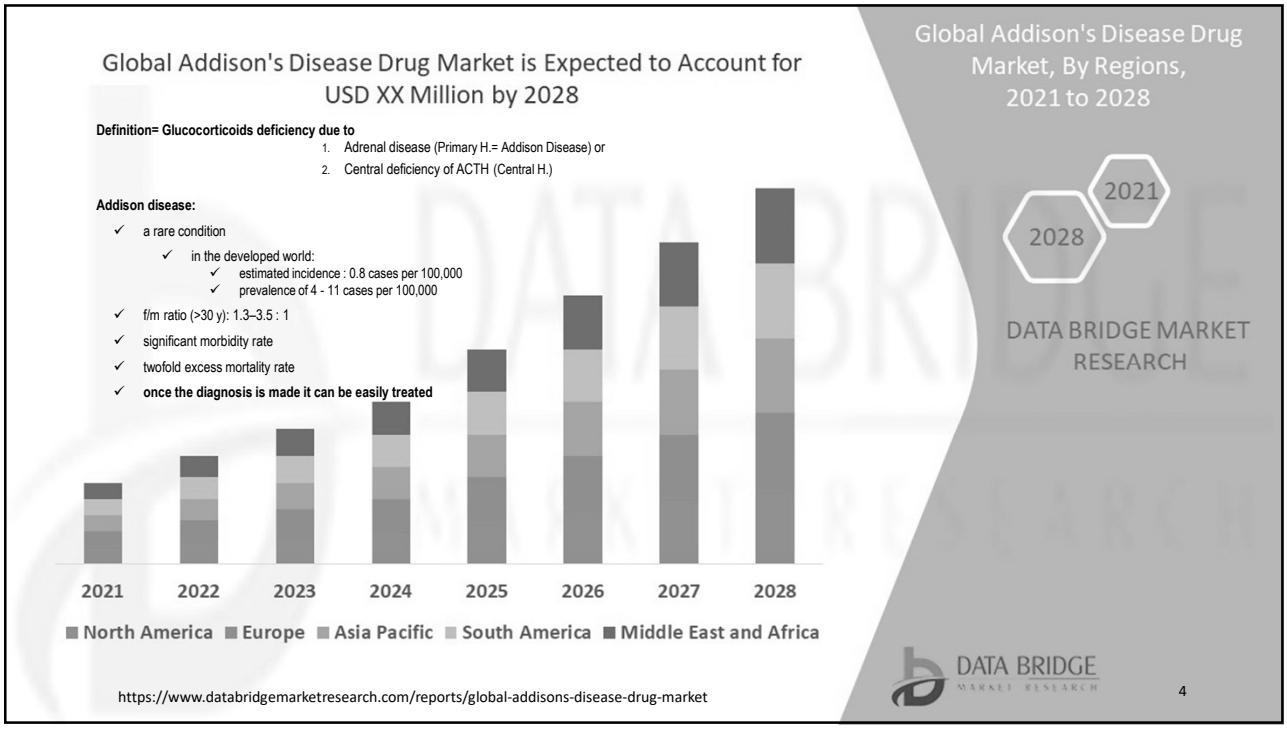
Definition= Glucocorticoids Deficiency due to

1. Adrenal disease (Primary H.= Addison Disease) or
2. Central deficiency of ACTH (Central H.)

Addison Disease Epidemiology:

- ✓ a rare condition
  - ✓ in the developed world:
    - ✓ estimated incidence : 0.8 cases per 100,000
    - ✓ prevalence of 4 - 11 cases per 100,000
- ✓ f/m ratio (>30 y): 1.3–3.5 : 1
- ✓ significant morbidity rate
- ✓ twofold excess mortality rate
- ✓ **once the diagnosis is made it can be easily treated**

3

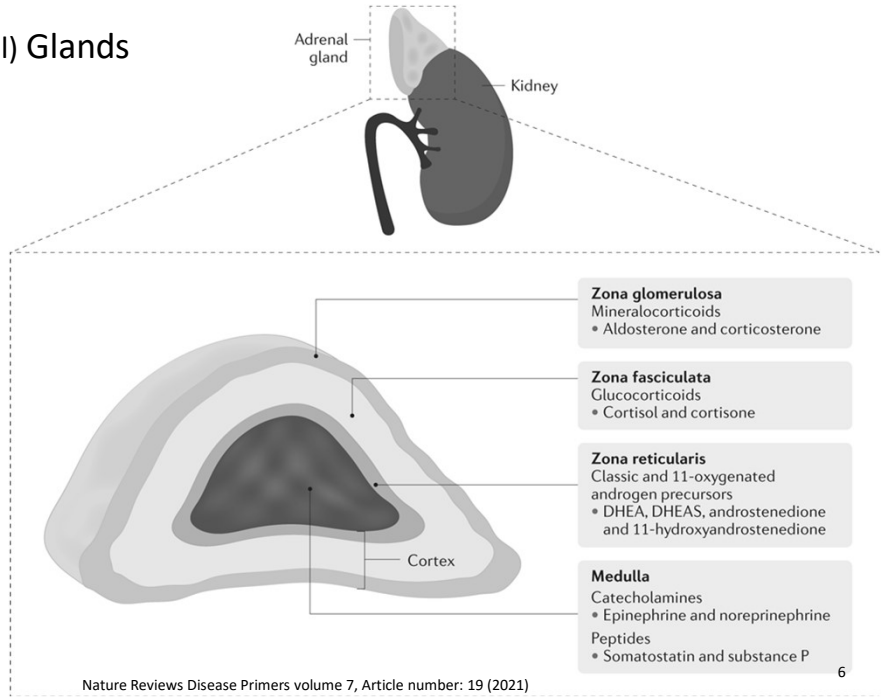


4

Healthy Adrenals

5

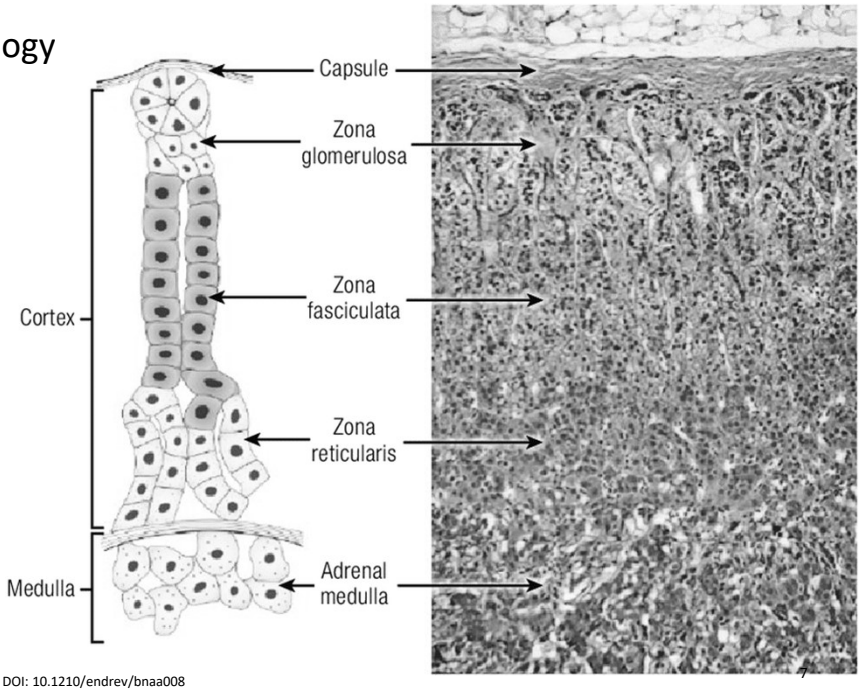
Adrenal (Suprarenal) Glands



Nature Reviews Disease Primers volume 7, Article number: 19 (2021)

6

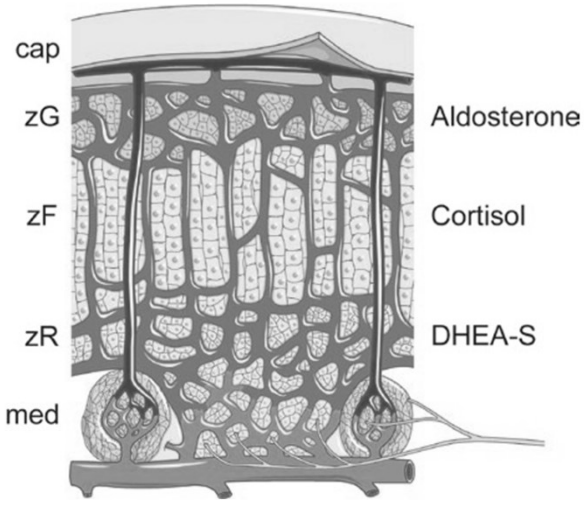
Adrenal Glands Histology



DOI: 10.1210/endrev/bnaa008

7

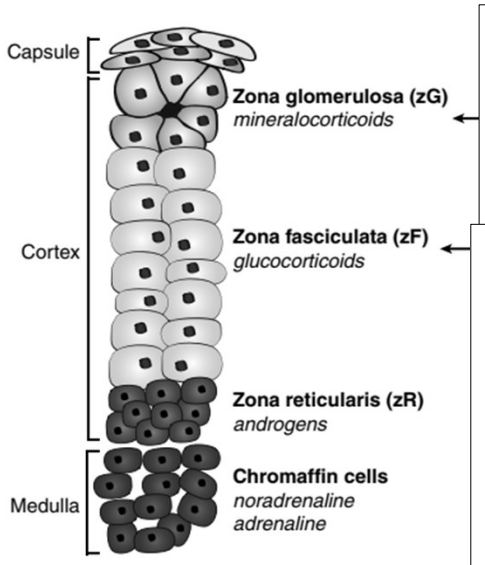
Adrenal Gland Vascularization



ENDOCRINOLOGY, Basic Science and Clinical Practice. R. Paul Robertson, 8th 2023

8

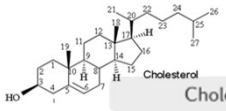
Regulation of Adrenal Cortex



CRH

9

Adrenal Steroidogenesis



Cholesterol

Cholesterol side-chain Cleavage Enxyme

Pregnenolone

17-α-OH-ase

Progesterone

21-α-OH-ase

11-Deoxycorticosterone

11-β-OH-ase

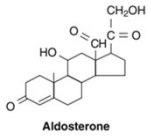
Corticosterone

18-Hydroxy-corticosterone

Aldosterone Synthase

Aldosterone

Mineralocorticoids
(zona glomerulosa)



Aldosterone

Cellular location of Enzymes

Mitochondria

SER

Nature Reviews Disease Primers volume 7, Article number: 19 (2021)

10

Adrenal Insufficiency

11

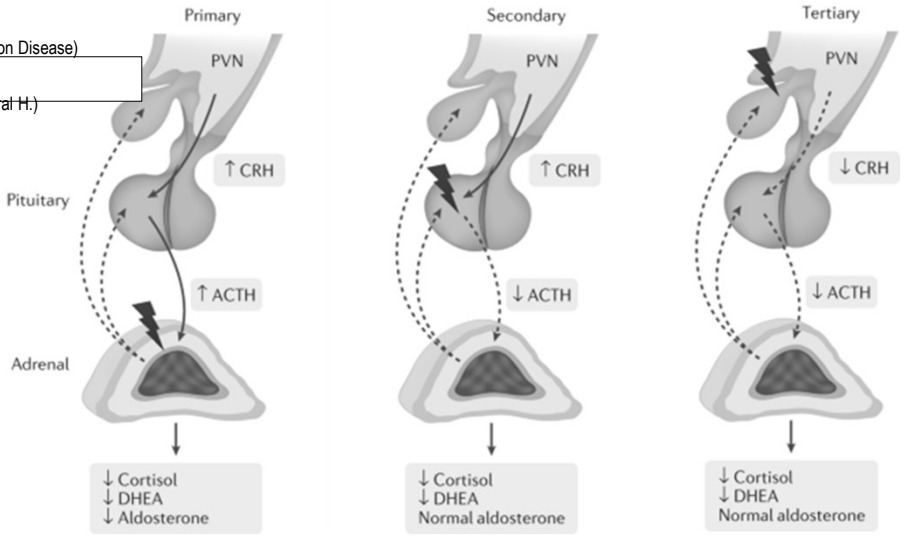
Classification of Adrenal Insufficiencies

1. Adrenal disease (Primary H.= Addison Disease)
2. Central deficiency of ACTH (Central H.)
    1. Secondary
    2. Tertiary

12

Classification of Adrenal Insufficiencies

1. Adrenal disease (Primary H.= Addison Disease)
2. Central deficiency of ACTH (Central H.)
   1. Secondary
   2. Tertiary



Nature Reviews Disease Primers volume 7, Article number: 19 (2021)

13

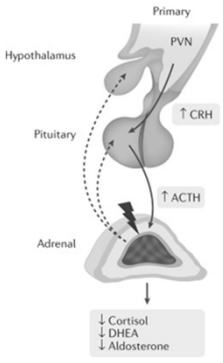


TABLE 93.1 Causes of Primary Adrenal Insufficiency

Diagnosis	Pathogenesis
Autoimmune Adrenal Insufficiency	
Infectious	
Genetic Disorders	
Familial Glucocorticoid Deficiency	

ENDOCRINOLOGY, Basic Science and Clinical Practice. R. Paul Robertson, 8th 2023

14

TABLE 93.2 Features of Autoimmune Polyendocrine Syndrome (APS)-I, APS-II, and X-Linked Polyendocrinopathy

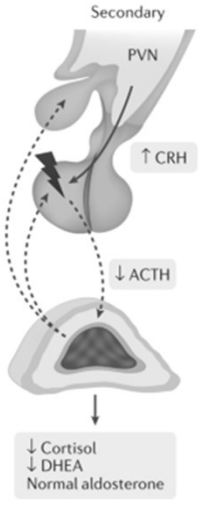
Features	APS-I	APS-II	X-Linked Polyendocrinopathy Immune Dysfunction and Diarrhea
Prevalence	Rare	Common	Very rare
Time of onset	Infancy	Adulthood	Neonatal period
Genetic and inheritance	Monogenic, *AIRE*	Polygenic	*FOXP2*, X-linked
Immunodeficiency	Asplenism, susceptibility to candidiasis	None	Overwhelming autoimmunity Loss of regulatory T-cells
Adrenal insufficiency	60%–70%	40%–50%	+
Diabetes mellitus	<20%	50%–60%	80%
Autoimmune thyroid disease	10%	70%–75%	+
Premature ovarian failure		Up to 21%	
Hypoparathyroidism	80%–85%	0%–5%	–
Mucocutaneous candidiasis	70%–80%	Nil	–
Male hypogonadism	12%	Rare	–
Hypopituitarism	0%–2%	<0.1%	–
Chronic active hepatitis	+	Rare	+
Pernicious anemia	+	0.1%–10%	–
Skin manifestation	Vitiligo, alopecia 10%–15%	Vitiligo, 5%–10%	Eczema, psoriasis, or atopic dermatitis
Gastrointestinal	Diarrhea, constipation	Celiac, 4%–9%	Enteropathy, malabsorption

ENDOCRINOLOGY, Basic Science and Clinical Practice. R. Paul Robertson, 8th 2023

15

TABLE 93.3 Causes of Secondary Adrenal Insufficiency

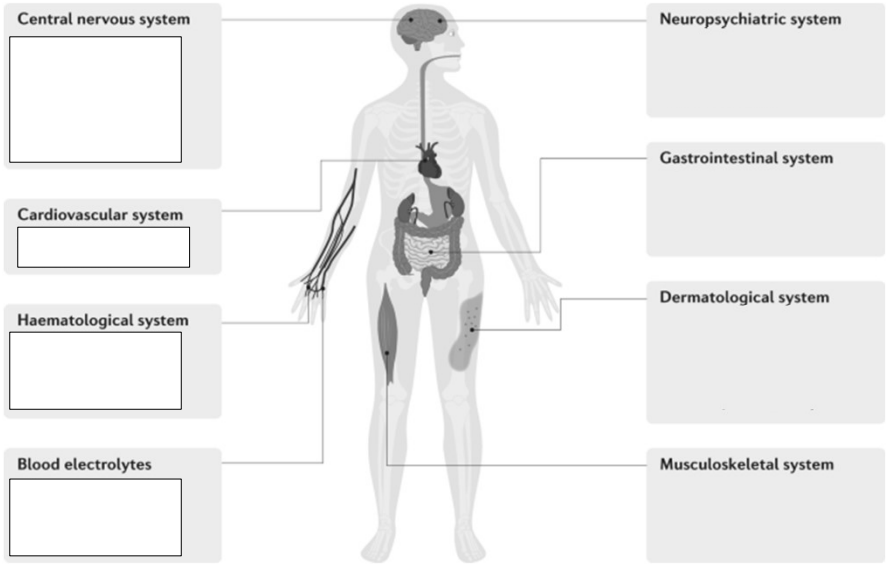
1. Hypothalamic-pituitary-adrenal suppression
2. Lesions of the hypothalamus or pituitary gland
3. Sarcoid
4. Head trauma
5. Isolated deficiency of ACTH



ENDOCRINOLOGY, Basic Science and Clinical Practice. R. Paul Robertson, 8th 2023

16

Clinical Manifestations of Adrenal Insufficiency



Nature Reviews Disease Primers volume 7, Article number: 19 (2021)

17

Clinical & Laboratory Features of Primary Adrenal Insufficiency

Feature	Frequency (%)
Symptoms	
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	13

Feature	Frequency (%)
Signs	
Weight loss	100
Hyperpigmentation	94
Hypotension (<110 mm Hg systolic)	88-94
Vitiligo	10-20
Auricular calcification	5

Feature	Frequency (%)
Laboratory Findings	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

Williams Textbook of ENDOCRINOLOGY, 14th 2020

18

Clinical & Laboratory Features of Primary Adrenal Insufficiency

Feature	Frequency (%)
Signs	
Weight loss	100
Hyperpigmentation	94
Hypotension (<110 mm Hg systolic)	88-94
Vitiligo	10-20
Auricular calcification	5

Feature	Frequency (%)
Symptoms	
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	13

Feature	Frequency (%)
Laboratory Findings	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

Williams Textbook of ENDOCRINOLOGY, 14th 2020

19

Clinical & Laboratory Features of Primary Adrenal Insufficiency

Feature	Frequency (%)
Laboratory Findings	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

Feature	Frequency (%)
Symptoms	
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	13

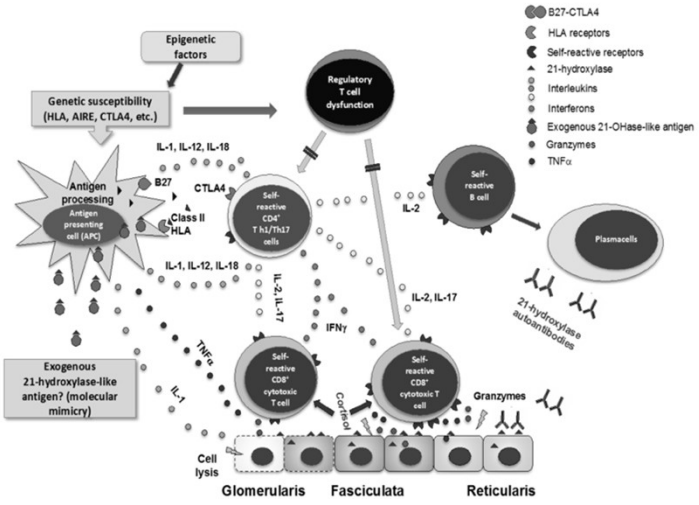
Feature	Frequency (%)
Signs	
Weight loss	100
Hyperpigmentation	94
Hypotension (<110 mm Hg systolic)	88-94
Vitiligo	10-20
Auricular calcification	5

Williams Textbook of ENDOCRINOLOGY, 14th 2020

20

Mechanisms of Autoimmune Adrenalitis

1. Unknown exogenous Ags (viruses, bacteria, chemicals) cross reactive with 21-hydroxylase may activate Ag Presenting Cells.
2. APCs process and present 21-OH-like Ags to Th1 / Th17.
3. T-helper cells promote activation and clonal expansion of cytotoxic T-lymphocytes to exogenous Ag, also of autoreactive cytotoxic CD8+ T-cells and autoreactive B cells which release self-destructive cytokines and steroid 21-OH autoantibodies (21-OHAbs), respectively.
4. This self-reactive process might be allowed by possible deficiency in T-regulatory (T-reg) cells.
5. The progressive destruction of glomerular, fascicular, and reticular cells of adrenal cortex is mediated by cytotoxic T cells through local production of cytokines.
6. Invitro: 21-OHAbs may also activate the complement system and antibody-dependent cellular cytotoxicity.
7. Local release of cortisol by zona fasciculata may hamper or delay this process

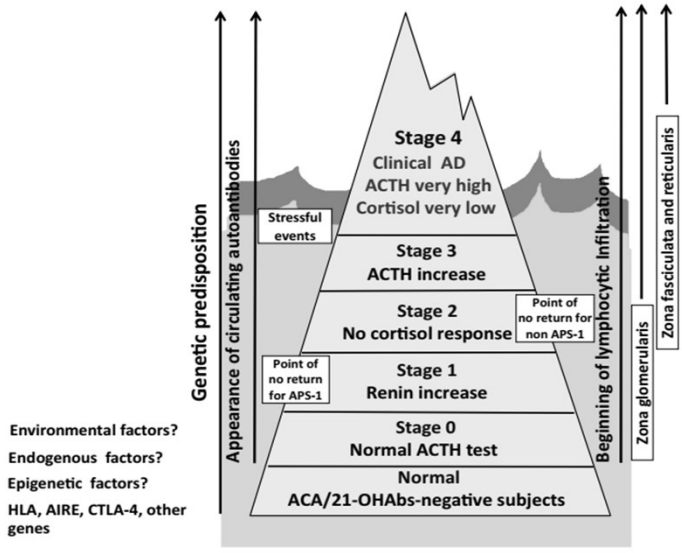


Epidemiology, pathogenesis, and diagnosis of Addison's disease in adults. Journal of Endocrinological Investigation. 2019

21

The natural history of autoimmune Addison's disease in adults

(From subclinical to clinically overt stage)



Epidemiology, pathogenesis, and diagnosis of Addison's disease in adults. Journal of Endocrinological Investigation. 2019

22

Stages of Adrenal Dysfunction in the Natural History of AAD

Autoimmune Addison's disease	Stage	ACA and/or 21-OHAbs	Symptoms	Plasma renin	Plasma aldosterone	Plasma ACTH	Plasma cortisol	Plasma cortisol after i.v. ACTH (250 µg)
Potential	0	+	Absent	N	N	N	N	N

*Below 500 nmol/L. N, normal range.

The natural history of autoimmune Addison's disease from the detection of autoantibodies to development of the disease: a long-term follow-up study on 143 patients. Eur J Endo, 2019

23

Laboratory Diagnosis

24

Table 1
Stages of Loss of Adrenal Function in Adrenal Antibody–Positive Patients[a]

Stage	Laboratory findings
0	Adrenal autoantibodies
1	Increased renin with low or normal aldosterone
2	Decreased response to ACTH stimulation
3	Persistently elevated ACTH
4	Low cortisol

Abbreviation: ACTH = adrenocorticotropic hormone.
[a] From Betterle et al (2).

Addison's Disease in Evolution: An Illustrative Case and Literature-ENDOCRINE PRACTICE Vol 20 No. 9 September 2014

25

Consensus statement on the diagnosis, treatment and follow-up of patients with Primary Adrenal Insufficiency

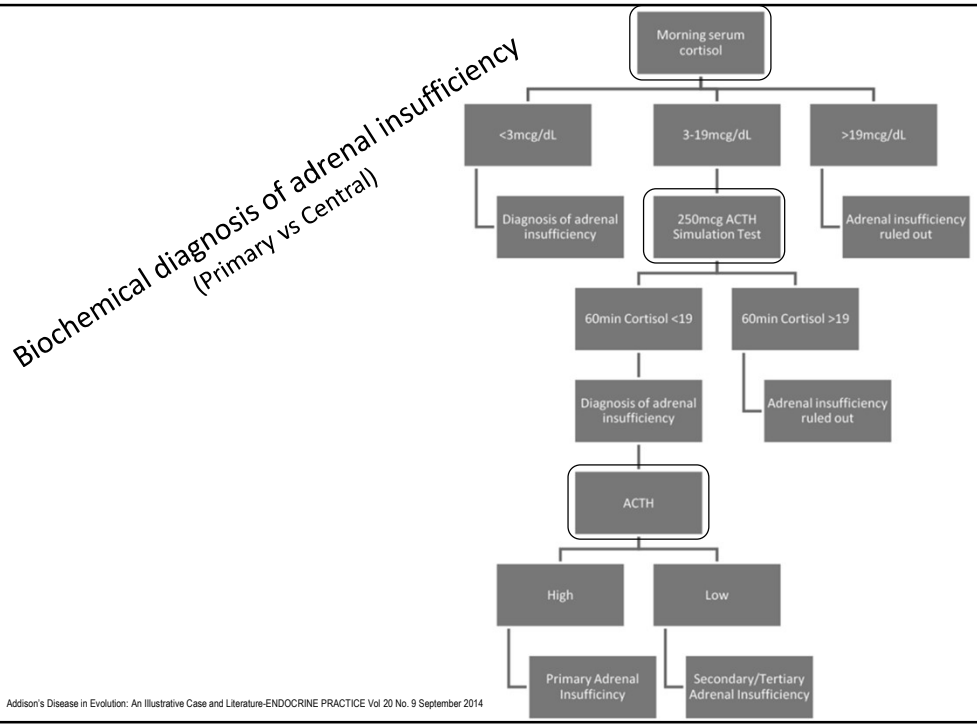
Table 1 *Summary of recommendations*

Area	No	Recommendation*
Diagnosis	1	The diagnosis of PAI should be considered in all patients presenting with unexplained collapse, hypotension, vomiting or diarrhoea. Hyperpigmentation, hyponatraemia, hyperkalaemia, acidosis and hypoglycaemia increase clinical suspicion of PAI
	2	Treatment of suspected acute adrenal insufficiency should never be delayed by diagnostic procedures
	3	The diagnostic test for primary PAI should be paired measurement of serum cortisol and plasma ACTH. In equivocal cases, a synacthen (tetracosactide) stimulated (0.25 mg im or iv) peak serum cortisol <500 nmol L^{-1} is diagnostic of PAI
	4	S-cortisol <250 nmol L^{-1} and increased ACTH in the presence of acute illness (suspected acute adrenal insufficiency) is diagnostic of primary PAI. S-cortisol <400 nmol L^{-1} and increased ACTH in the presence of acute illness raises a strong suspicion of PAI

Consensus statement on the diagnosis, treatment ad follow-up of patients with primary adrenal insufficiency. Journal of Internal Medicine, 2013
(European Consortium& the Endocrine Society Clinical Practice Guideline)

26

Biochemical diagnosis of adrenal insufficiency (Primary vs Central)



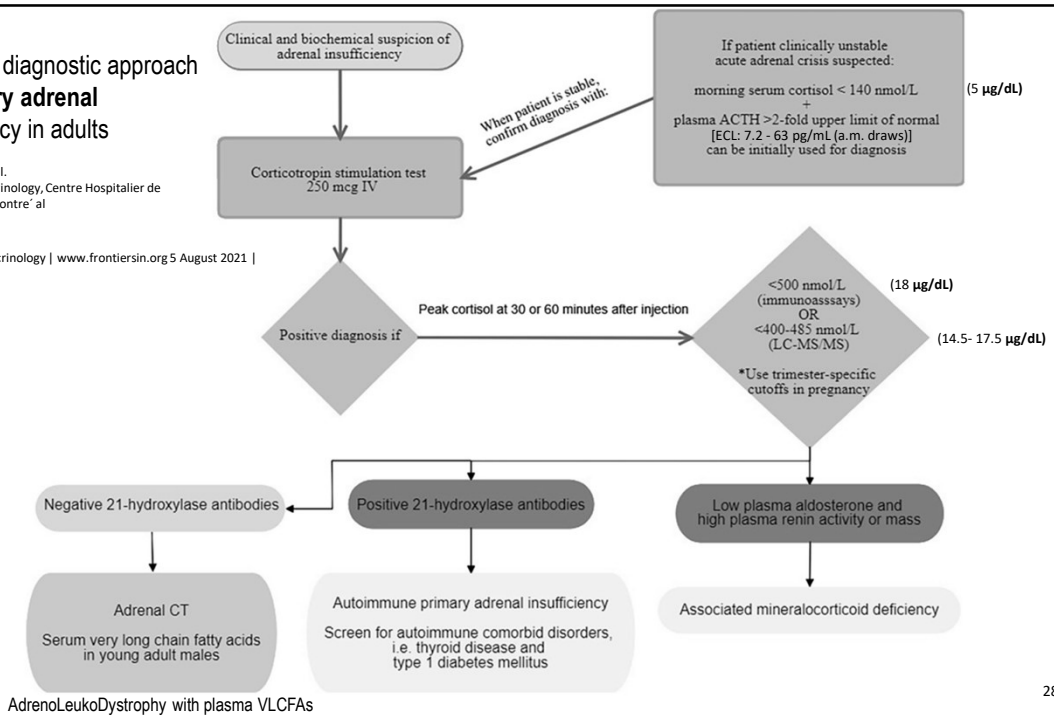
Addison's Disease in Evolution: An Illustrative Case and Literature-ENDOCRINE PRACTICE Vol 20 No. 9 September 2014

27

Proposed diagnostic approach for **primary adrenal** insufficiency in adults

Andre Lacroix et al.
Division of Endocrinology, Centre Hospitalier de l'Universite´ de Montre´ al
QC, Canada

Frontiers in Endocrinology | www.frontiersin.org 5 August 2021 |



AdrenoLeukoDystrophy with plasma VLCFAs

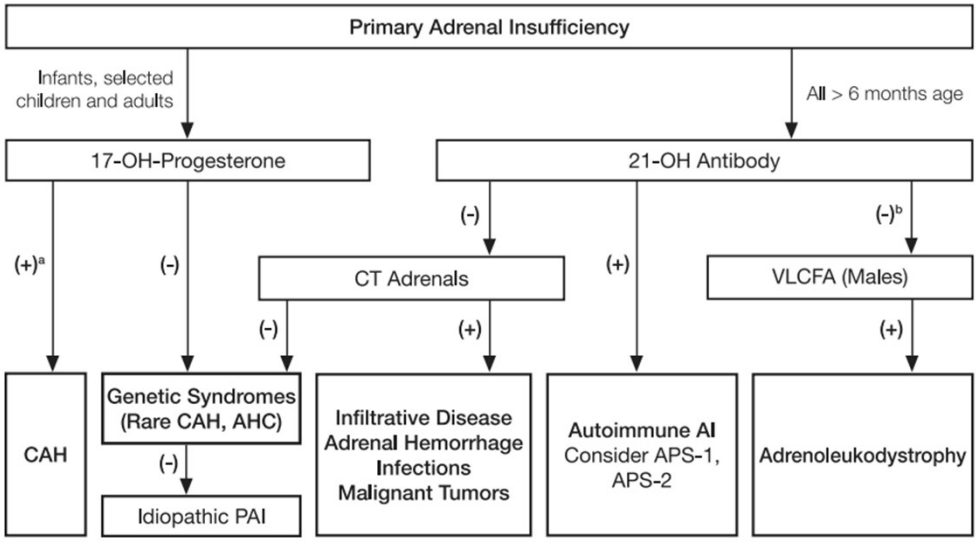
28

Laboratory Tests for Differential Diagnosis of Adrenal Insufficiencies

	Lab Tests				
Adrenal Insufficiency	**Cortisol 8 am**	**ACTH**	**Cortisol after ACTH**	**Cortisol after CRH**	**ACTH after CRH**
Primary	Low	High	No Response	No Response	Highly Rise
Secondary	Low	Low	Rise	No Response	No Response
Tertiary	Low	Low	Rise	Rise	Rise

29

Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline



J Clin Endocrinol Metab, Feb. 2016, 101(2):364–389

30

Reference Values

FREE CORTISOL

6-10:30 a.m. Collection: 0.121 - 1.065 µ /dL

TOTAL CORTISOL

5 - 25 µ/dL (a.m.)

2 - 14 µ /dL (p.m.)

Pediatric reference ranges are the same as adults, as confirmed by peer-reviewed literature.

ACTH

7.2 - 63 pg/mL (a.m. draws)

No established reference values for p.m. draws

Pediatric reference values are the same as adults, as confirmed by peer reviewed literature

17-Hydroxyprogesterone

Males: <220 ng/dL

Females Follicular: <80 ng/dL Luteal: <285 ng/dL Postmenopausal: <51 ng/dL

MayoClinic-2023

		Biological Variation			Desirable specification		
Sample	Analyte	CV_g	CV_i	II	I(%)	B(%)	TE(%)
Serum	Cortisol	15.2	38.1	0.4	7.6	10.26	22.8
Plasma	ACTH						
Serum	17-HydroxyProgesterone	19.6	50.4	0.38	9.8	13.5	29.7

https://www.westgard.com/biodatabase1.htm-2023

31

ACTH assay Collection Instructions:

1. Morning (6 a.m.-10:30 a.m.) specimen is desirable.
2. Collect with a pre-chilled lavender top (EDTA) tube and transport to the laboratory on ice.
3. Centrifuge at refrigerated temperature within 2 hours and immediately separate plasma from cells.
4. Immediately freeze plasma

32

Thank You for Your Attention

dr.bakhtiari.academy

33