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Il Pediatra tra Famiglia,
Protocolli e Linee Guida

11 - 18 Luglio 2008

Clinica Pediatrica
Università degli Studi
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2) ADDISON

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TABLE 1. Etiology of adrenocortical insufficiency or AD

Primary adrenocortical insufficiency
1. Autoimmune adrenalitis
2. Infectious adrenalitis
   - Tuberculosis
   - Fungal
   - Viral (HIV, CMV)
3. Neoplastic diseases
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   - Congenital adrenal hypoplasia
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     - Familial glucocorticoid deficiency
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   - Kearns-Sayre syndrome
   - Congenital adrenal hyperplasia
   - Smith-Lemli-Opitz syndrome

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Insufficienza surrenalica

Primitiva = Morbo di Addison

1) Forme autoimmuni	65- 70%
2) Tubercolosi	25- 50%

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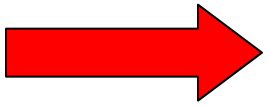

Insufficienza surrenalica

Primitiva = Morbo di Addison

1) Forme autoimmuni	65- 70%
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3) Adrenoleucodistrofia X-linked	10- 20%

ADRENOLEUCODISTROFIA

ADRENOLEUKODYSTROPHY (ALD) is an X-linked genetic disorder characterized by adrenal insufficiency and demyelination within the central nervous system .

The biochemical defect of ALD is characterized by impaired oxidation of very long chain fatty acids (VLCFA), particularly hexacosanoic acid (C26:0), pentacosanoic acid (C25:0), and tetracosanoic acid (C24:0), which accumulate in tissues and body fluids.

The ALD gene has been mapped to Xq28.

The importance of testing for adrenoleucodystrophy in males with idiopathic Addison's disease

M D Ronghe, J Barton, P E Jardine, E C Crowne, M H Webster, M Armitage, J T Allen, C G Steward

Arch Dis Child 2002;86:185–189

Table 1 Phenotypes seen in male X-ALD patients

Phenotype	Age of onset	Estimated relative frequency
Childhood cerebral	3–10 years	31–35%
Adolescent	11–21 years	4–7%
Adrenomyeloneuropathy	19–37 years	40–46%
Adult cerebral	Adulthood	2–5%
Olivopontocerebellar	Adolescence or adulthood	1–2%
Addison's only	Common before 7.5 years	Varies with age; up to 50% in childhood
Asymptomatic	Biochemical abnormality only	Diminishes with age
		Common <4 years
		Very rare >40 years

Adapted from Moser *et al*.[1]

X-Linked Adrenoleukodystrophy Is a Frequent Cause of Idiopathic Addison's Disease in Young Adult Male Patients

STEFANO LAURETI, GIOVANNI CASUCCI, FAUSTO SANTEUSANIO, GABRIELLA ANGELETTI, PATRICK AUBOURG, AND PAOLO BRUNETTI

TABLE 5. In this table were combined the data from Sadeghi-Nejad (27), Jorge (28), and Table 1

	Sadeghi-Nejad	Jorge	This study	Total
Population studied (no. of idiopathic Addison)	8	24	14	46
No. of ALD patients identified (%)	5/8 (62)	5/24 (20)	5/14 (35)	15/46 (32)
Age (yr) at onset of Addison[a]				
Mean ± SD	4.5 ± 4.4	10 ± 3.7	20.4 ± 10.1	11.6 ± 9.2
Range	(1–12)	(4–14)	(12–32)	(1–32)
Age (yr) at diagnosis of Addison[a]				
Mean ± SD	7.5 ± 4.8	ND	21.8 ± 11.6	14.6 ± 11.3
Range	(1.5–15)	ND	(12–36)	(1.5–36)
Secondary onset of neurological symptoms[a]	2/5	3/5	3/5	8/15

ND, not determined.
[a] ALD patients.

JCEM 1996

Insufficienza surrenalica

Primitiva = Morbo di Addison

1) Forme autoimmuni	65- 70%
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3) Adrenoleucodistrofia X-linked	10- 20%
4) Forme rare, genetiche	2- 5%

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DAX-1, an Unusual Orphan Receptor at the Crossroads of Steroidogenic Function and Sexual Differentiation

ENZO LALLI AND PAOLO SASSONE-CORSI

Molecular Endocrinology 17: 1445–1453, 2003

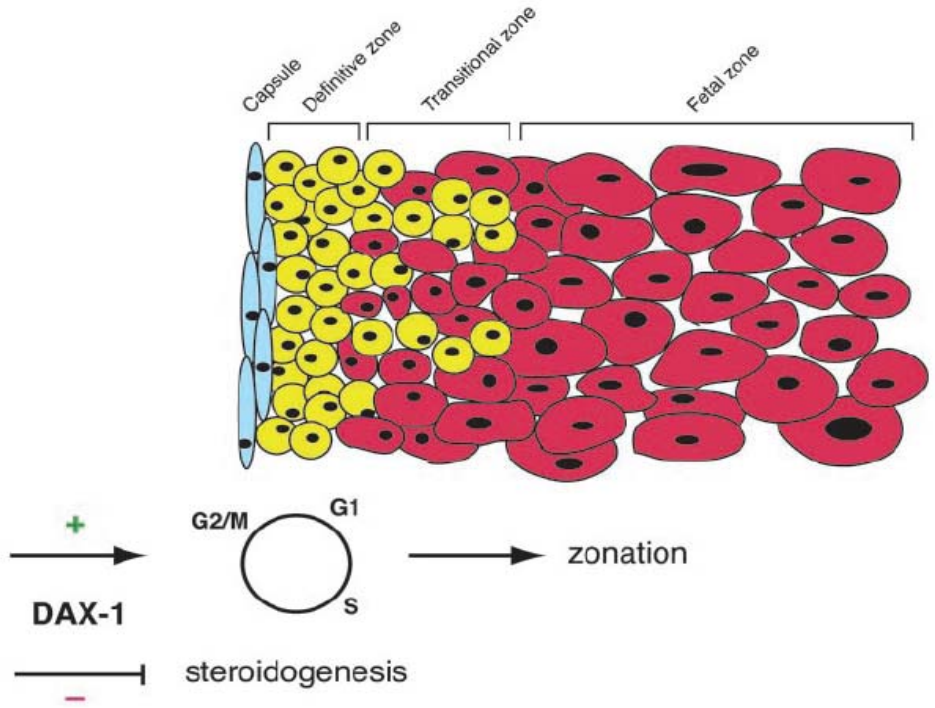


Fig. 2. A Model of DAX-1 Function during Human Adrenal Development

DAX-1 represses steroidogenic gene expression in definitive zone cells, allowing for their proliferation and differentiation into glomerulosa, fasciculate, and reticularis zones. In the absence of functional DAX-1, abnormally early expression of steroidogenic genes is activated in the definitive zone and its proliferation is down-regulated. Under these conditions, adrenal hypoplasia follows the physiological regression of the fetal zone.

Molecular mechanisms of DAX1 action

Anita K. Iyer[a], Edward R.B. McCabe[a,b,c,d,e,*]

Molecular Genetics and Metabolism 83 (2004) 60–73

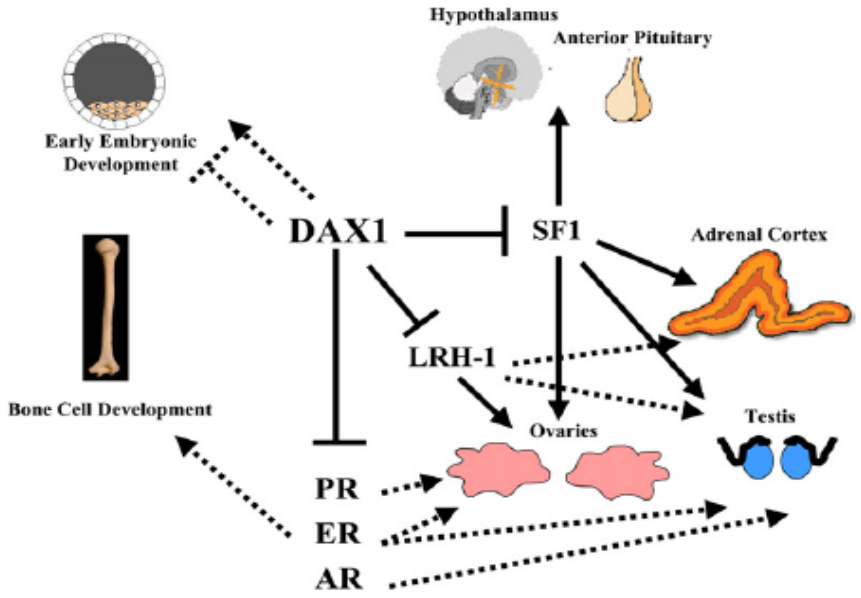


Fig. 4. Role of DAX1 and mechanisms of action. DAX1 may have pleiotropic roles in early embryonic development, bone cell development, and HPAG axis development and adult function, and may repress the action of various nuclear receptors depending on cellular and physiological context. Solid lines show definitive stimulatory and inhibitory relationships. Dotted lines indicate relationships where tissue coexpression has been shown, but functional activity remains to be determined. See text for details.

Congenital Adrenal Hypoplasia: Clinical Spectrum, Experience with Hormonal Diagnosis, and Report on New Point Mutations of the DAX-1 Gene

MICHAEL PETER, MATTHIAS VIEMANN, CARL-JOACHIM PARTSCH, AND WOLFGANG G. SIPPELL

J Clin Endocrinol Metab **83:** 2666–2674, 1998

TABLE 1. Clinical characteristics of 18 AHC boys

Case no.	Age at onset of symptoms	First symptoms	Cryptorchidism/ hypogonadotropic hypogonadism	Phenotype	Family history	Remarks
1	1 month	Salt-wasting	No/prepubertal	AHC	Unknown	
2	2 weeks	Salt-wasting	Yes/-	AHC, GKD, DMD	Unknown	Died at age 1 yr in Addisonian crisis
3	2 months	Salt-wasting	?/prepubertal	AHC	Unknown	
4	3 weeks	Salt-wasting	Yes/prepubertal	AHC, GKD, DMD	Yes	
5	1 month	Salt-wasting	Yes/prepubertal	AHC	Yes	Severe brain damage after convulsions, initial diagnosis CAH (21-hydroxylase def)
6	3 weeks	Salt-wasting	No/-	AHC	Yes	Died at age 6 yr in Addisonian crisis, initial diagnosis CAH (11-hydroxylase def)
7	1 month	Salt-wasting	?/-	AHC, GKD, DMD	Unknown	Died at age 4 months
8	3 years	Salt-wasting	No/prepubertal	AHC, GKD	Yes	Diagnosed after younger brother (case 9)
9	1 month	Salt-wasting	No/prepubertal	AHC, GKD	Yes	Younger brother of case 8
10	2 weeks	Salt-wasting	Yes/prepubertal	AHC	Unknown	Low maternal estriol levels during pregnancy, initial diagnosis CAH (11-hydroxylase def)
11	1 month	Salt-wasting	?/HH	AHC	Unknown	Initial diagnosis CAH (21-hydroxylase def)
12	2 weeks	Salt-wasting	Yes/HH	AHC	No	
13	2 weeks	Salt-wasting	?/HH	AHC	Unknown	Initial diagnosis CAH (21-hydroxylase def)
14	2 weeks	Salt-wasting	?/prepubertal	AHC, GKD, DMD	No	
15	5 months	Hypoglycemic convulsion	Yes/prepubertal	AHC	Yes	Low maternal estriol levels during pregnancy, older brother of case 16
16	Treatment started in the first week	Any	No/prepubertal	AHC	Yes	Low maternal estriol levels during pregnancy, younger brother of case 15
17	1 week	Salt-wasting	Yes/HH	AHC	Yes	
18	2 weeks	Salt-wasting	No/prepubertal	AHC	No	

CASO CLINICO

Mattia (4 anni e 4 mesi), giunge a ricovero c/o la Clinica Pediatrica per comparsa di vomito da circa due giorni.

Obiettività all'ingresso:

- cute pallida, fredda e sudata
- occhi alonati
- restante obiettività negativa
- Sat O2 98 %, FC 130 bpm

Esami ematochimici all'ingresso:

- EAB: ph 7.25, Bicarbonati 19.9 mEq/L; EB –7, SO2 41% (venoso)
- emocromo: GB 20.480/mmc (N 73%, L 20%), pst 822.000/mmc;
- Na: 114 mEq/L; Cl 80 mEq/L; K 5.3 mEq/L; Ca 11.3 mEq/L; urea 90 mg/dl.

Alla luce degli esami è stata intrapresa infusione e.v. con dapprima soluzioni isotoniche (sol. fisiologica 0.9 % e glucosata 5%), quindi ipertoniche.
Per il persistere dell'iponatremia è stata introdotta terapia con Idrocortisone a dosi elevate.

Si è assistito a successiva normalizzazione della sodiemia e notevole miglioramento del quadro clinico del paziente.

La terapia con idrocortisone è stata continuata a dosaggi più bassi durante il ricovero con successiva aggiunta di fludrocortisone.

Nel sospetto di un'insufficienza surrenalica, sono stati eseguiti ulteriori indagini ematochimiche, test da stimolo con ACTH, indagini strumentali e genetiche.

…… anamnesi negativa

Anamnesi fisiologica:

- Nato a termine mediante parto eutocico da gravidanza normodecorsa
- PN: 3.540 kg; LN 52 cm; CC 35 cm. Adattamento neonatale e sviluppo psicomotorio nella norma nella norma

Anamnesi patologica:

Non riferiti disturbi degni di nota.

Anamnesi familiare:

Non riferiti disturbi degni di nota a carico di entrambi i genitori e dei nonni (eccetto per il nonno materno affetto da ipertensione in terapia medica).

…… dati auxologici

Peso adeguato all'altezza. Stadi puberali adeguati all'età cronologica.

Età ossea 6 aa e 6/12 secondo metodoTanner e 5-6 aa secondo metodo Greulich e Pyle.

Esami ematochimici eseguiti in corso di degenza:

- 17-OHP, TSH, fT3, fT4, Ab anti-tireoglobulina e anti-tireoperossidasi, Insulina, PTH, Aldosterone: *nella norma*.
- *degni di nota*: ACTH 222 pg/ml; Progesterone <0.64 nmol/L; Prolattina 31.4 ng/ml
- acidi grassi a lunga catena: *nella norma.*
- autoanticorpi: anti-stomaco, anti-surrene, anti-insula pancreatica, anti-ipofisi, anti-cute, anti-DNA, anti-mitocondrio, anti-LKM, anti-ribosoma, anti-reticolina: *negativi*; anti-nucleo fegato/rene 160 (vn <20); anti-21 idrossilasi e anti-cellule producenti steroidi in corso.

ACTH test:

tempi	*-30'*	*0'*	*60'*	*120'*	
cortisolo	14.8	15.1	11.1	8.24	µg/dl
testosterone	< 0.69			< 0.69	nmol/l
DHEA-S	< 15	< 15	< 15	< 15	µg/dl
androstenedione	0.01	0.01	0.01	0.01	ng/ml
17-OHP	0.21	0.22	0.28	0.20	ng/ml

***Indagini strumentali**:*

- *ETG addome superiore ed inferiore*: nella norma.
- *RMN encefalo, senza e con mdc*: “modesta alterazione di segnale in sede peritrigonale bilaterale” per il resto nella norma. *Conclusioni:* il rilievo descritto in sede peritrigonale appare in relazione alla presenza di spazi perivascolari dilatati/aree terminali di mielinizzazione.
- *RMN addome superiore, senza e con mdc*: nella norma.

Analisi molecolare del gene DAX1 per insufficienza surrenalica:

Mattia: *delezione del nucleotide g.186delC in emizigosi, codone prematuro di terminazione (PTC) aminoacido 264.*

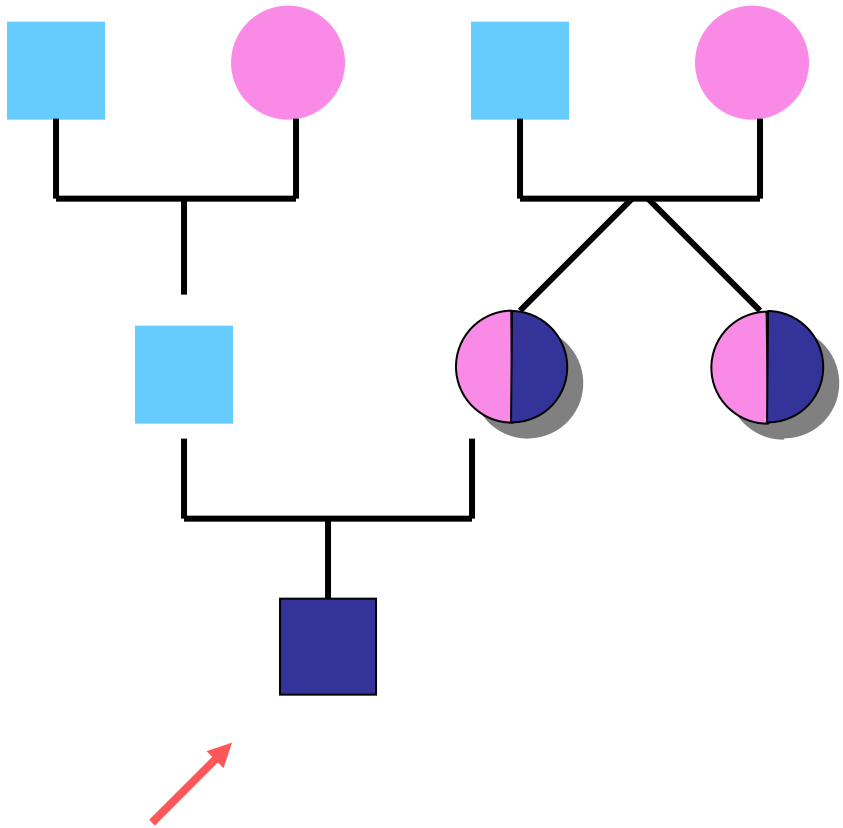
Conclusione: **genotipo emizigote per la mutazione patologica g.186delC.**

Madre: *delezione del nucleotide g.186delC in emizigosi, codone prematuro di terminazione (PTC) aminoacido 264.*

Conclusione: **genotipo eterozigote per la mutazione patologica g.186delC.**

Padre: *Conclusione:* **genotipo compatibile con allele normale per la regione indagata**

NB: sorella gemella della madre di Mattia affetta dallo stesso tipo di mutazione NROB1.



…… in conclusione

Diagnosi di dimissione

Insufficienza surrenalica congenita

Terapia alla dimissione:

- **Idrocortisone**
- **Fludrocortisone**

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Nonclassic Congenital Lipoid Adrenal Hyperplasia: A New Disorder of the Steroidogenic Acute Regulatory Protein with Very Late Presentation and Normal Male Genitalia

Bo Y. Baker,* Lin Lin,* Chan J. Kim,* Jamal Raza, Claire P. Smith, Walter L. Miller, and John C. Achermann

TABLE 1. Clinical and biochemical characteristics of patients with nonclassic lipoid CAH

	Val187Met	Arg188Cys		Normal range
	Patient 1	Patient 2	Patient 3	
Age at investigation (yr)	4.5	2.2	2.8	
Presentation	Hypoglycemia, pigmentation	Pigmentation	Pigmentation	
Adrenal imaging	Normal US	Normal CT	Normal CT	
ACTH (pg/ml)	>1250	>1250	>1250	10–50
Cortisol				
Basal (μg/dl)	<1.0	6.2	11.3	5–15
Peak (μg/dl)	<1.0	5.6	10.5	>20
PRA (ng/ml/h)	5.3	5.4	20.2	0.3–3.9
Aldosterone (ng/dl)	15.5	6.7	12.4	4–31
Treatment	Hydrocortisone	Hydrocortisone, fludrocortisone	Hydrocortisone, fludrocortisone	

Conversion to Systeme International units: ACTH, picograms per milliliter × 0.22 for picomoles per liter; cortisol, micrograms per deciliter × 27.6 for nanomoles per liter; PRA, nanograms per milliliter per hour × 0.77 for picomoles per milliliter per hour; aldosterone, nanograms per deciliter × 27.7 for picomoles per liter. US, Ultrasound scan.

J Clin Endocrinol Metab 2006

N Engl J Med 1996

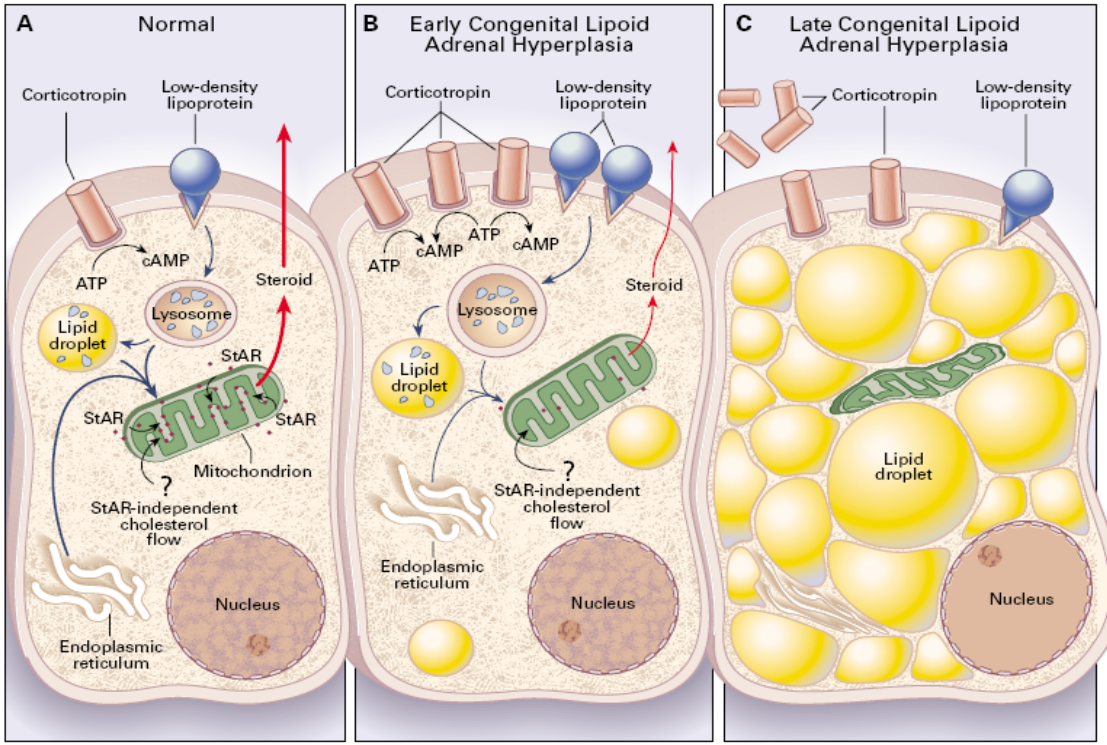

Figure 3. Model of Congenital Lipoid Adrenal Hyperplasia in an Adrenal Cell.

In the normal cell (Panel A), cholesterol is derived by endogenous synthesis from acetyl–coenzyme A in the endoplasmic reticulum, from cholesterol esters stored in lipid droplets, and from low-density lipoprotein cholesterol, which after receptor-mediated endocytosis, is processed in lysosomes before it is used or stored in lipid droplets. Cholesterol is transported to the outer mitochondrial membrane by ill-defined processes involving the cytoskeleton.[35] The rate-limiting step in steroidogenesis is the movement of cholesterol from the outer to the inner mitochondrial membrane; this can be promoted by steroidogenic acute regulatory protein (StAR), but may also be mediated by mechanisms independent of this protein. Thus, the net synthesis of steroid is due to mechanisms dependent on, as well as independent of, the protein. In Panel B, in the absence of steroidogenic acute regulatory protein, as in early congenital lipoid adrenal hyperplasia or in a placental cell, mechanisms independent of the protein can still move some cholesterol into the mitochondria, resulting in a low level of steroidogenesis. In patients with affected adrenal cells this results in increased corticotropin secretion, stimulating further production of cholesterol and its accumulation as cholesterol esters in lipid droplets. In Panel C, as lipid droplets accumulate they engorge the cell, damaging its cytoarchitecture through both physical displacement and the chemical action of cholesterol auto-oxidation products. Steroidogenic capacity is destroyed, and consequently tropic stimulation continues. In the ovary, follicular cells remain unstimulated and, hence, undamaged until they are recruited at the beginning of each menstrual cycle. Small amounts of estradiol are produced, as shown in Panel B, effecting phenotypic feminization and vaginal bleeding, but the cycles are anovulatory, resulting in infertility and progressive hypergonadotropic hypogonadism. cAMP denotes cyclic AMP.

Manifestazioni cliniche

• Melanodermia	90 - 100%
• Astenia, anoressia, dimagrimento	90%
• Dolori addominali, mialgie	70-90%
• Ipotensione arteriosa	70%
• Ipoglicemia, iponatremia, iperkaliemia	30- 50%
• Amenorrea secondaria	30%
• Riduzione peluria pubica ed ascellare	25%
• Turbe neuropsichiche	50%

Segni di allarme: vomito, diarrea, febbre

↓

CRISI SURRENALICA

Diagnostica ormonale nel morbo di Addison

TEST da stimolo con ACTH

	basale	dopo 60 min
Cortisolo (mcg/dl)	< 3 (v.n. 6-24)	< 3 (v.n. picco > 20)
ACTH (pg/ml)	> 100 (v.n. < 40)	

Importante
Nella forma secondaria il cortisolo è basso ma dosabile,
l'ACTH è basso e manca la melanodermia

Diagnostica di forma

Autoimmunità

1) Anti - 17 - idrossilasi (17OHAb) : 10-15%

2) Anti – 21 - idrossilasi (21OHAb) : 85- 90%

3) Anti - colesterolo desmolasi (P450sccAb) : 10-15%

4) Anti - cellule steroidee (StCA) : 15- 25%

Terapia

Sostitutiva

1) Hydrocortisone 25 mg/m2/die in 3 somministrazioni
oppure
Cortisone acetato 32 mg/m2/die in 2 o 3 somministrazioni
(2/3 mat e 1/3 pom)
2) Fluodrocortisone 0.05- 0.15 mg/die unica somministrazione

Emergenza

1) Sol. NaCl 0.9% + glucosio 5% alla velocità di 10-20ml/kg per 1- 2 ore
2) Idrocortisone in bolo e.v.
25 mg nel lattante
50 mg nel bambino piccolo
100 mg nel bambino più grande e adolescente
continuare con idrocortisone e.v. 100 mg/m2/24 ore o i.m. diviso in 4 dosi
3) DOCA (desossicorticosterone acetato) 1-2 mg in bolo i.m.