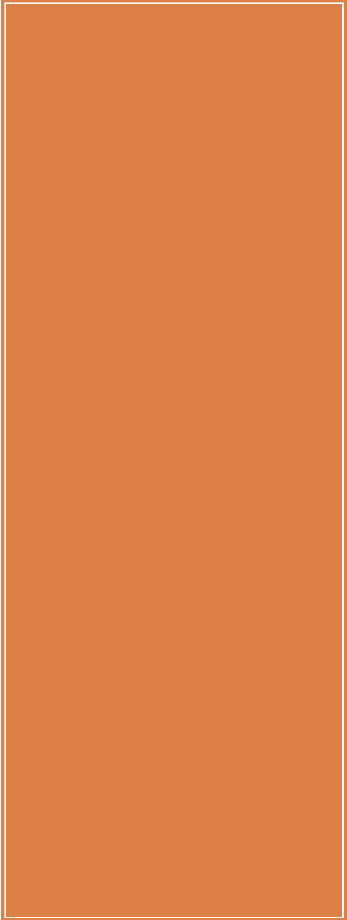


ABC - Altogether to Beat Cushing's syndrome

Il Cushing in età pediatrica : l'approccio diagnostico

Paola Loli
S.C. Endocrinologia
Ospedale Niguarda Cà Granda

epidemiologia

- 
- Incidenza: 0,7-2 casi/milione popol/anno
 - 10% casi pediatrici
 - Adenoma ipof ACTH secernente secondo per frequenza nell'infanzia

Sindrome di Cushing in età pediatrica - Eziologia

CS ACTH-dipendente

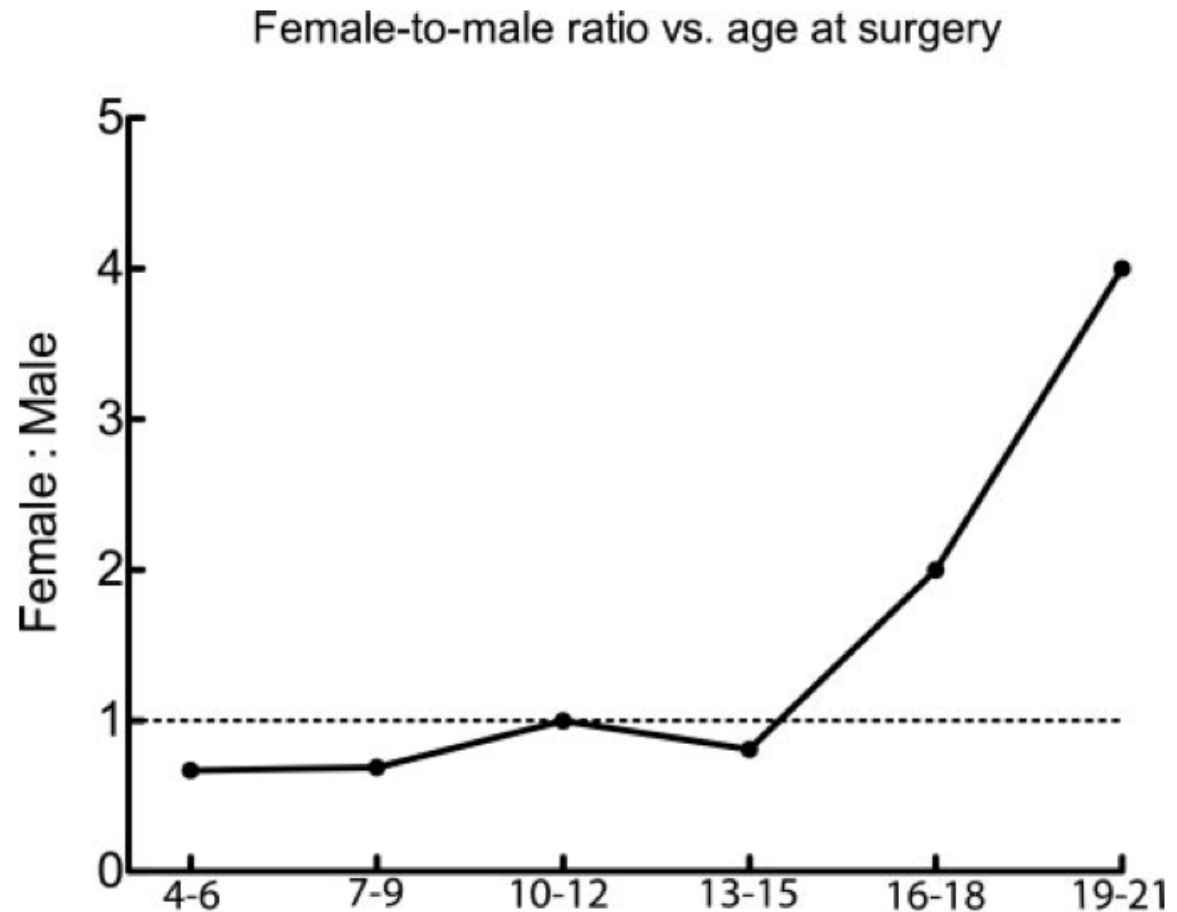
- M. di Cushing (adenoma ipofisario ACTH secernente)
- Sindrome da ACTH ectopico

CS ACTH-indipendente

- da steroidi esogeni (compresse, gocce nasali, spray nasali, pomate)
- da tumore corticosurrenalico (adenoma o carcinoma)
- Da iperplasia surrenalica primitiva:
 - ▣ PPNAD
 - ▣ Iperplasia surrenalica macronodulare
 - ▣ S. McCune-Albright

Outcome of Surgical Treatment of 200 Children With Cushing's Disease

Gender ratio
vs age at
surgery





INFANTILE IATROGENIC CUSHING'S SYNDROME

Selahattin Katar, Sedat Akdeniz,¹ M Nuri Özbek, and Ahmet Yaramiş

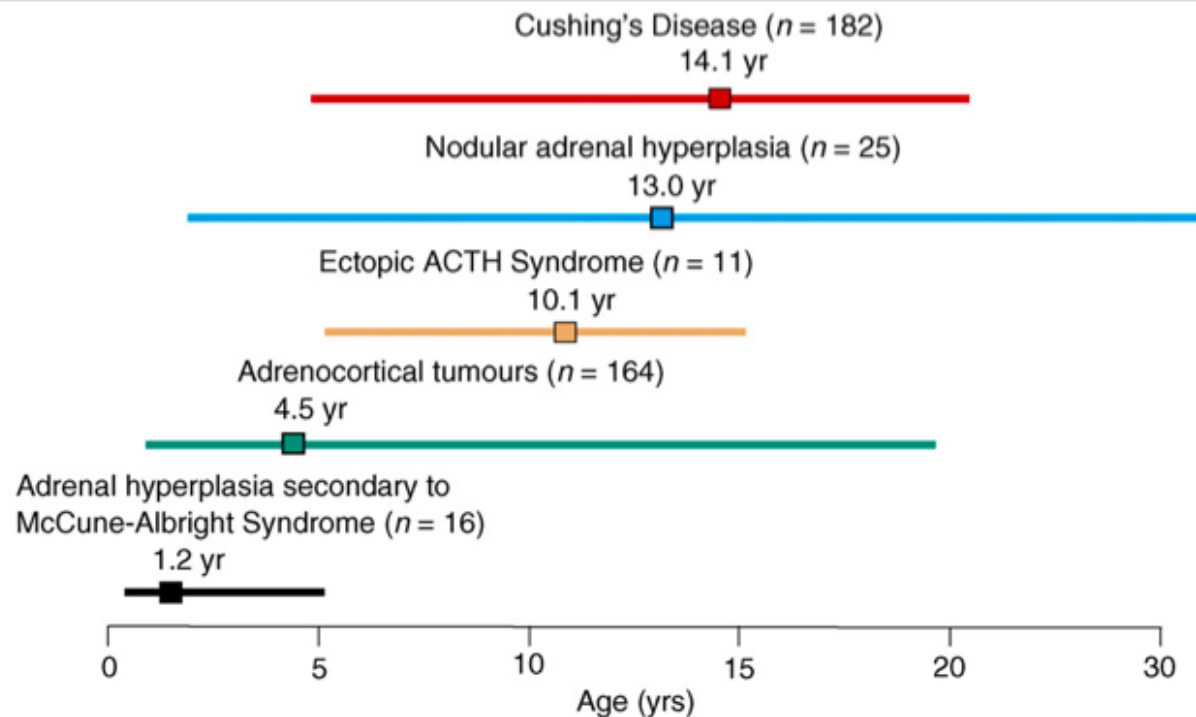
.....When parents were questioned for the details of patient's history, we learned **about the usage of pomade clobetasol-17-propionate (3 tubes, each of 30g). It was used two to three times in a day for the last 3 months for skin dryness.**

This product was purchased from drugstore without any prescription. The parents were not informed about the application period and possible side effects of the product



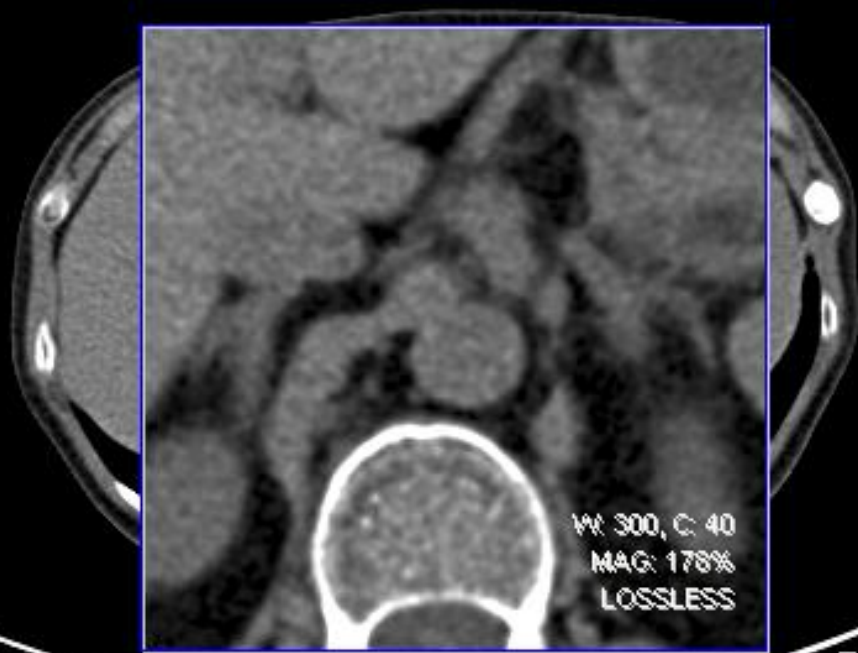
Cushingoid features of patient after 2 months of topical steroid application

Review of 398 pediatric CS cases from the literature showing ages of peak incidence, represented by the boxes

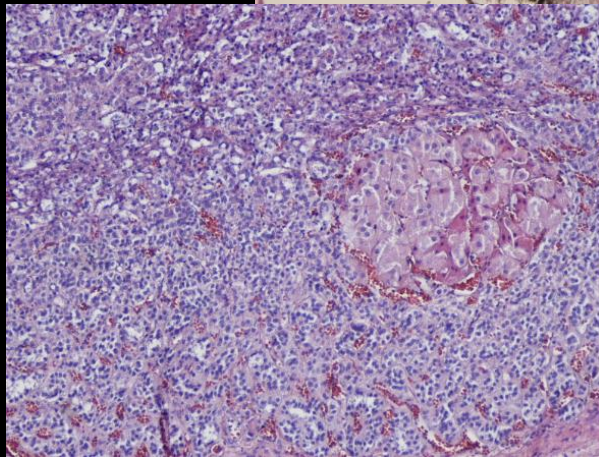
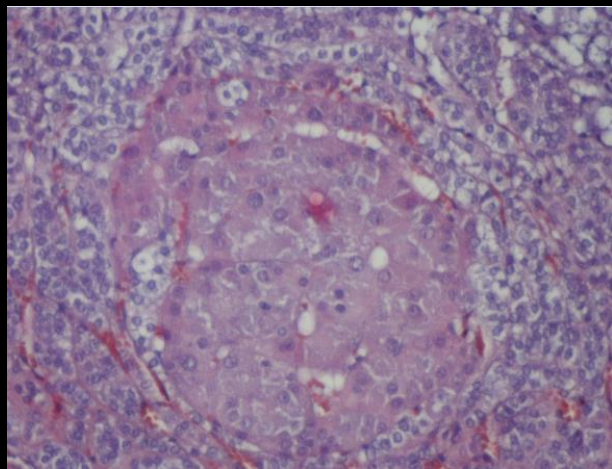
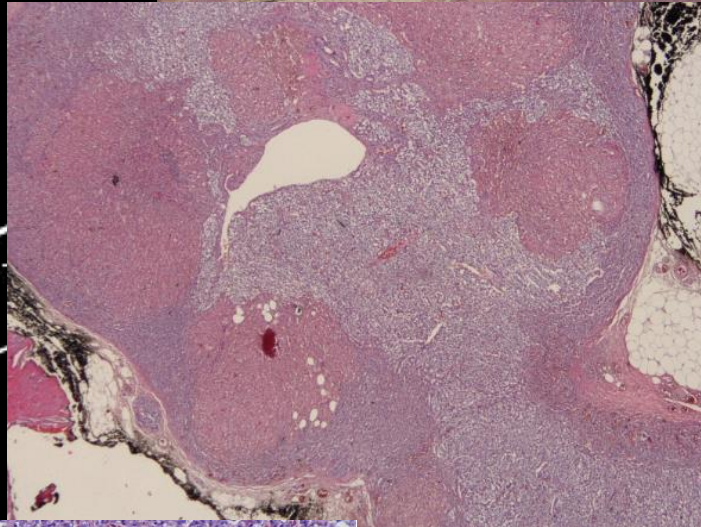
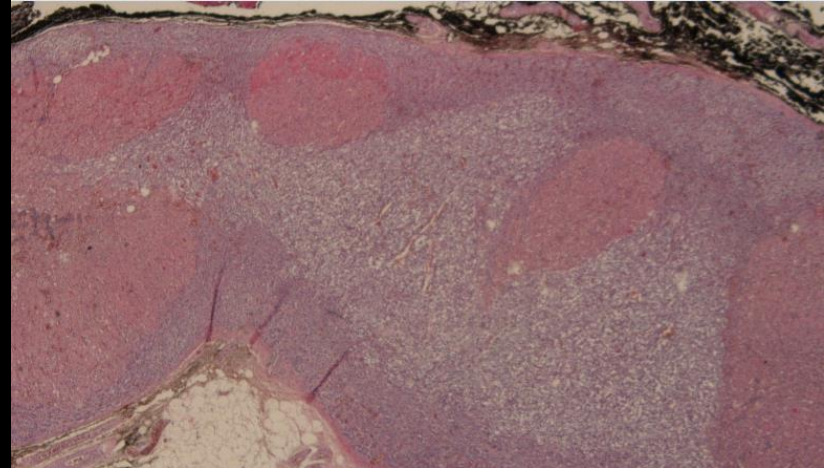


TRENDS in Endocrinology & Metabolism

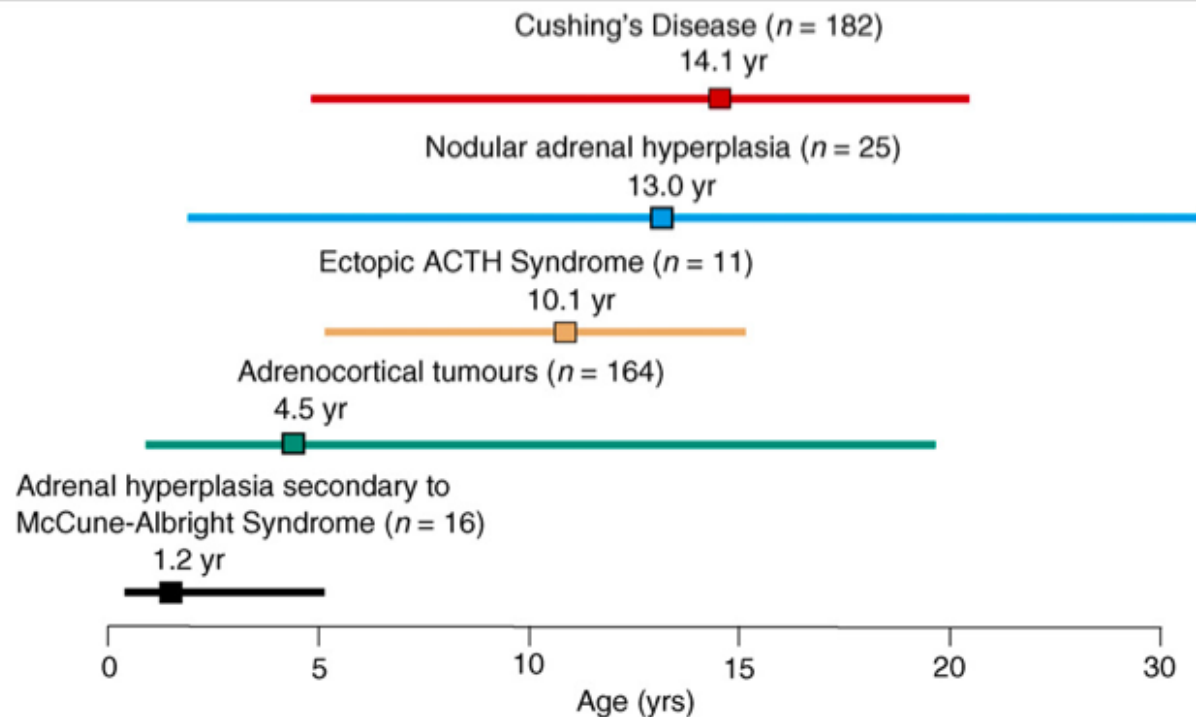
Figure 1. Different aetiologies of paediatric Cushing's syndrome from the literature ($n = 398$ cases) shown at ages of peak incidence (boxes).



TC



Review of 398 pediatric CS cases from the literature showing ages of peak incidence, represented by the boxes

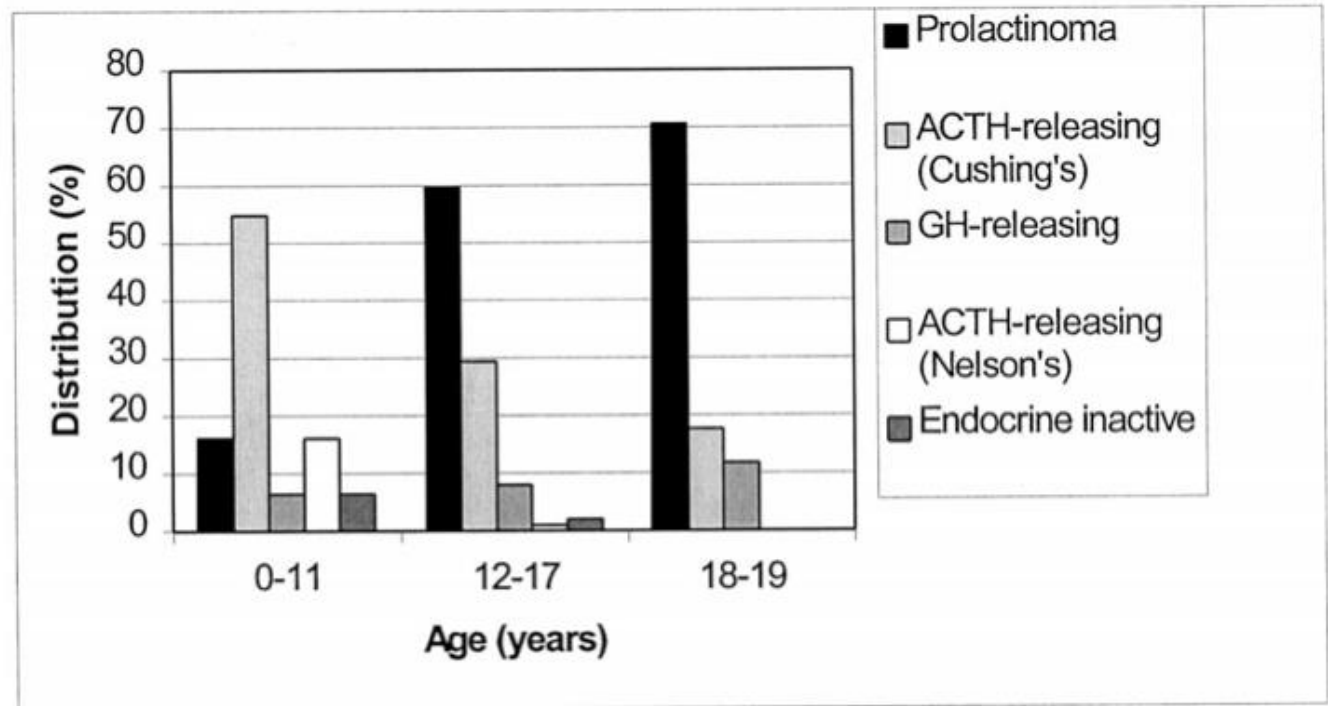


TRENDS in Endocrinology & Metabolism

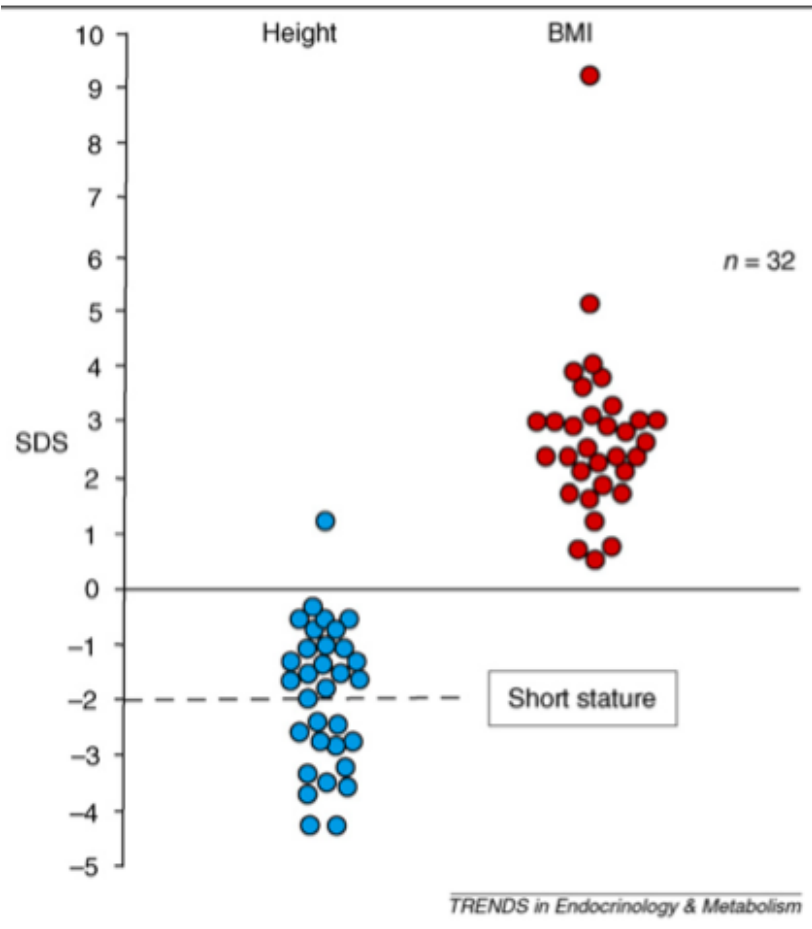
Figure 1. Different aetiologies of paediatric Cushing's syndrome from the literature ($n = 398$ cases) shown at ages of peak incidence (boxes).

Pediatric Pituitary Adenomas

Frequency of pituitary adenomas by age. The percentages in each age group add up to 100. The different adenoma types are listed in the same order for each age group.

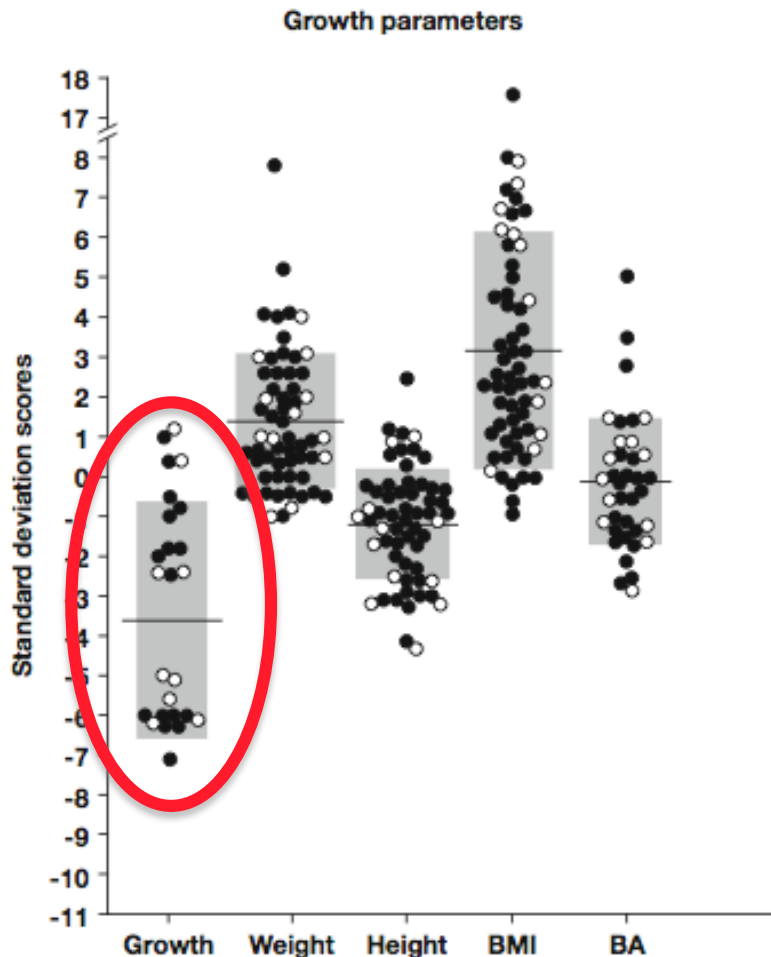


Paediatric Cushing's syndrome: epidemiology, investigation and therapeutic advances



Height (blue) and body mass index (BMI; red) SDS values in 32 paediatric patients with Cushing's disease. The dotted line indicates the SDS value below which patients are significantly shorter than average.

Cushing's syndrome in children and adolescents



Growth rate, weight, height, BMI, and bone age of 59 children and adolescents with Cushing syndrome, as compared with expected values for age and sex. The horizontal lines and the shaded bars indicate the means $\pm$ SD. The SD score is defined as the number of standard deviations of the mean of the values in normal subjects of the same age and sex by which the values in the patients differed from normal

SINTOMO O SEGNO	FREQUENZA (%)	SINTOMO O SEGNO	FREQUENZA (%)
Aumento di peso	90	iperpigmentazione	14
Ritardo di crescita	83	Ridotta forza muscolare	12
Irregolarità mestruali	78	Acantosi nigricans	12
irsutismo	78	Ritardo età ossea	11
obesità	75	Avanzamento età ossea	8
Striae rubrae	61	Disturbo del sonno	8
acne	47	ipercalcemia	7
ipertensione	47	alcalosi	7
Esauribilità/debolezza	44	Ritardo puberale	3
Anticipazione sviluppo puberale	38	ipokaliemia	2
Fragilità cutanea	25	epifisiolisi	2

Outcome of Surgical Treatment of 200 Children With Cushing's Disease

Table 2. Presenting Signs and Symptoms

Presenting Signs and Symptoms	Prepubertal Patients (n = 91)	Postpubertal Patients (n = 109)	All Patients (n = 200)
Rapid weight gain	88 (97)	98 (90)	186 (93)
Obesity ^a	81 (89)	59 (54)	140 (71)
Dorsal cervical or supraclavicular fat pad	58 (64)	79 (72)	137 (69)
Moon facies	56 (62)	70 (64)	126 (63)
Decreased linear growth ^b	77 (85)	48 (44)	125 (63)
Central obesity	57 (63)	66 (61)	123 (62)
Hirsutism	47 (52)	65 (60)	112 (56)
Abdominal striae ^b	39 (43)	70 (64)	109 (55)
Fatigue	43 (47)	52 (48)	95 (48)
Acne	44 (48)	50 (46)	94 (47)
Amenorrhea (primary or secondary) ^c	NA	49 (72)	52 (49)
Headaches	33 (36)	43 (39)	76 (38)
Hypertension	27 (30)	44 (40)	71 (36)
Acanthosis nigricans	32 (35)	32 (29)	64 (32)
Depression, anxiety, mood swings	22 (24)	39 (36)	61 (31)
Easy bruising ^b	14 (15)	35 (32)	49 (25)
Gynecomastia ^c	8 (15)	9 (22)	17 (16)
Glucose intolerance or diabetes	2 (2)	11 (10)	13 (7)
Alopecia	3 (3)	8 (7)	11 (6)
Bone fractures	3 (3)	4 (4)	7 (4)
Nephrolithiasis	1 (1)	6 (6)	7 (4)

Skeletal Maturation in Children with Cushing Syndrome Is Not Consistently Delayed: The Role of Corticotropin, Obesity, and Steroid Hormones, and the Effect of Surgical Cure

Table I. Baseline characteristics of children with CD and AICS

Characteristics	CD (n = 93)	AICS (n = 31)	P value
CA at time of preoperative BA, y, mean $\pm$ SD	12.3 $\pm$ 2.9	10.3 $\pm$ 4.5	.0223*
Females/males, n (%)	43 (46.2)/ 50 (53.8)	22 (71.0)/ 9 (29.0)	.0221*
Race, n (%)			.7981
Asian	4 (4.3)	2 (6.5)	
Black	6 (6.4)	3 (9.7)	
White	61 (65.6)	21 (67.7)	
Other/unknown	22 (23.7)	5 (16.1)	
Ethnicity, n (%)			.3301
Latino or Hispanic	24 (25.8)	5 (16.1)	
Not Latino or Hispanic	66 (71.0)	26 (83.9)	
Unknown	3 (3.2)	0	
Duration of symptoms until surgery, mo, mean $\pm$ SD	32.5 $\pm$ 21.0	26.2 $\pm$ 25.1	.0178*
BMI z-score, mean $\pm$ SD	2.3 $\pm$ 0.6	2.1 $\pm$ 0.7	.0742
Height SDS, mean $\pm$ SD	-1.1 $\pm$ 1.2	-1.1 $\pm$ 1.6	.9872
Breast tanner stage (females), median (IQR)	3.0 (3.0-5.0)	2.5 (1.0-4.5)	.0741
Testicular volume by Prader orchidometer (males), cc, median (IQR)	8.0 (5.4-10.0)	4.5 (2.5-15.0)	.1663
BA, y, mean $\pm$ SD	12.8 $\pm$ 2.9	10.7 $\pm$ 4.6	.0312*
BA - CA (difference, y), mean $\pm$ SD	0.5 $\pm$ 1.3	0.4 $\pm$ 1.4	.4861
BAZ, mean $\pm$ SD	0.6 $\pm$ 1.4	0.5 $\pm$ 1.8	.8865
ACTH, pg/mL, mean $\pm$ SD	53 $\pm$ 44	6 $\pm$ 3	< .0001*
IGF-1 z-score, mean $\pm$ SD	-0.4 $\pm$ 1.6	0.1 $\pm$ 1.8	.1495
DHEA, ng/dL, mean $\pm$ SD	595 $\pm$ 502	156 $\pm$ 253	< .0001*

Table I. Baseline characteristics of children with CD and AICS

Characteristics	CD (n = 93)	AICS (n = 31)	P value
DHEAS, μ g/dL, mean $\pm$ SD	236 $\pm$ 203	63 $\pm$ 83	< .0001*
Normalized ratio of mean for age and sex, DHEAS, mean $\pm$ SD	2.2 $\pm$ 2.0	0.9 $\pm$ 0.8	< .0001*
Androstenedione, ng/dL, mean $\pm$ SD	142 $\pm$ 118	146 $\pm$ 101	.7952
Normalized ratio of mean for age and sex, androstenedione,	2.6 $\pm$ 2.3	4.4 $\pm$ 8.2	.2031
E2, pg/mL	23 $\pm$ 31	31 $\pm$ 44	.2376
Normalized ratio of mean for age and sex, E2, mean $\pm$ SD	1.4 $\pm$ 1.2	1.7 $\pm$ 1.4	.31
Testosterone, ng/dL, mean $\pm$ SD	74 $\pm$ 137	40 $\pm$ 70	.0471*
Normalized ratio of mean for age and sex, testosterone, mean $\pm$ SD	1.2 $\pm$ 1.2	1.4 $\pm$ 1.2	.1869
UFC, μ g/24 h, mean $\pm$ SD	322 $\pm$ 353	286 $\pm$ 259	.2548
Midnight cortisol, μ g/dL, mean $\pm$ SD	19.7 $\pm$ 15.0	20.5 $\pm$ 13.6	.7329
Fasting insulin μ U/mL, mean $\pm$ SD	34.2 $\pm$ 33.6	25.4 $\pm$ 13.9	.4611
BMI z-score, mean $\pm$ SD	2.1 $\pm$ 0.7	2.3 $\pm$ 0.7	.196

Skeletal Maturation in Children with Cushing Syndrome Is Not Consistently Delayed: The Role of Corticotropin, Obesity, and Steroid Hormones, and the Effect of Surgical Cure

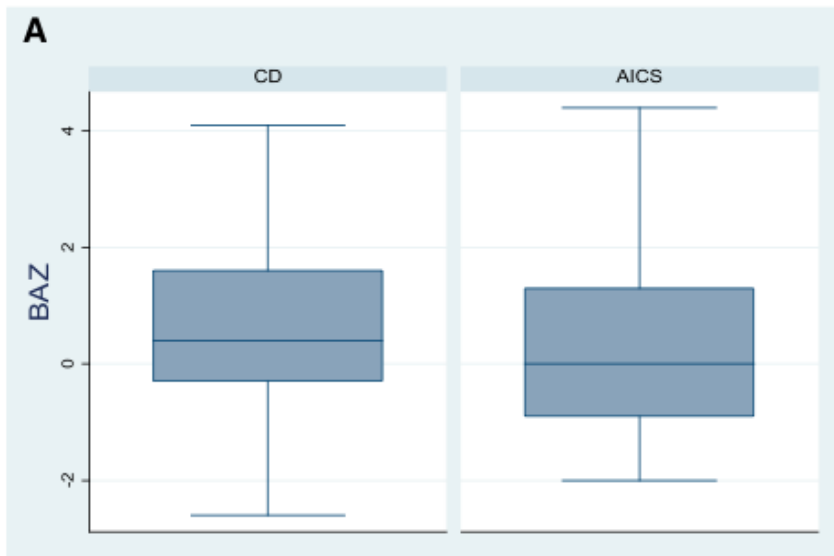
Table II. Clinical characteristics of patients with CS and advanced BA or normal/delayed BA

Characteristics	Advanced BAZ (n = 26)	Normal/delayed BAZ (n = 98)	P value
CA at time of preoperative BA, y, mean $\pm$ SD	9.9 $\pm$ 2.5	12.3 $\pm$ 3.5	.0001*
Duration of symptoms, mo, mean $\pm$ SD	36.7 $\pm$ 25.5	29.4 $\pm$ 21.1	.1150
Height SDS, mean $\pm$ SD	-0.3 $\pm$ 1.1	-1.3 $\pm$ 1.3	.0005*
Breast tanner stage (females), median (IQR)	3.0 (1.0-4.0)	3.0 (2.0-5.0)	.0679
Testicular volume by Prader orchidometry (males), cc, median (IQR)	6.5 (6.0-8.0)	8.5 (4.5-20.0)	.3327
ACTH, pg/mL, mean $\pm$ SD	52 $\pm$ 69	39 $\pm$ 33	.5367
IGF-1 z-score, mean $\pm$ SD	0.7 $\pm$ 1.8	-0.6 $\pm$ 1.5	.0004*
DHEAS, μ g/dL, mean $\pm$ SD	206 $\pm$ 212	189 $\pm$ 192	.5117
Normalized ratio of mean for age and sex, DHEAS, mean $\pm$ SD	3.2 $\pm$ 2.8	1.5 $\pm$ 1.3	.0001*
DHEA, ng/dL, mean $\pm$ SD	566 $\pm$ 622	457 $\pm$ 445	.5973
Normalized ratio of mean for age and sex, DHEA, mean $\pm$ SD	2.9 $\pm$ 2.6	1.6 $\pm$ 1.5	.0054*
Androstenedione, ng/dL, mean $\pm$ SD	140 $\pm$ 95	144 $\pm$ 119	.8382
Normalized ratio of mean for age and sex, androstenedione, mean $\pm$ SD	4.2 $\pm$ 3.0	2.8 $\pm$ 4.9	.0010*
E2, pg/mL, mean $\pm$ SD	25 $\pm$ 42	24 $\pm$ 32	.4574
Normalized ratio of mean for age and sex, E2, mean $\pm$ SD	1.8 $\pm$ 1.1	1.3 $\pm$ 1.1	.016*
Testosterone, ng/dL, mean $\pm$ SD	32 $\pm$ 36	76 $\pm$ 139	.0553
Normalized ratio of mean for age and sex, testosterone, mean $\pm$ SD	1.8 $\pm$ 1.4	1.1 $\pm$ 1.1	.0256*
UFC, μ g/24 h, mean $\pm$ SD	206 $\pm$ 201	343 $\pm$ 355	.0598
Midnight cortisol, μ g/dL, mean $\pm$ SD	17.3 $\pm$ 10.9	20.6 $\pm$ 15.5	.2623
Fasting insulin, μ U/mL, mean $\pm$ SD	47.0 $\pm$ 53.2	28.5 $\pm$ 19.6	.0651
BMI z-score, mean $\pm$ SD	2.4 $\pm$ 0.5	2.0 $\pm$ 0.7	.0146*

Skeletal Maturation in Children with Cushing Syndrome Is Not Consistently Delayed: The Role of Corticotropin, Obesity, and Steroid Hormones, and the Effect of Surgical Cure

Boxplot comparing baseline BAZ in children with CD and children with AICS (0.6 ` 1.4 vs 0.5 ` 1.8; $P = .8865$)

Boxplot comparing initial BAZ with BAZ at the 1-y follow-up after surgical cure of CS (1.0 ` 1.6 vs 0.3 ` 1.4; $P < .0001$)



Screening

Urinary free cortisol values in normal children and adolescents

Maria Teresa Gomez, MD, Saul Malozowski, MD, J. Winterer, MD,*
Nikos C. Vamvakopoulos, and George P. Chrousos

From the Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

Scanty information is available regarding normal urinary free cortisol excretion values in children. The few reports published provide valuable information but usually include small numbers of subjects or insufficient (5 to 12 hours) urine collections.¹⁻¹² The purpose of this study was to determine reference values for daily UFC excretion in a large population of healthy children matched by age, gender, size, and pubertal development, and to establish the correlations between 24-hour UFC values corrected by creatinine excretion, body surface area, and chronologic age. This information is needed for the evaluation of adrenocortical function in children with suspicion of disorders of the hypothalamic-pituitary-adrenal axis.

METHODS

One hundred eight healthy children (57 girls) partici-

Center Laboratory the day after the completion of the urine collection.

All children had a complete physical examination. Weight was determined with a regular scale. All heights were obtained with the use of a wall-mounted stadiometer. Body surface areas were determined according to the Gehan and George nomogram.¹³ Pubertal development was assessed according to Tanner.¹⁴ If a discrepancy between two clinical variables was present (e.g., pubic hair stage IV, breast development stage III), the highest value category was assigned.

UPC Urinary free cortisol

Laboratory study. Urinary free cortisol was determined with a specific direct radioimmunoassay (SmithKline

Diagnostic Tests for Children Who Are Referred for the Investigation of Cushing Syndrome

UFC

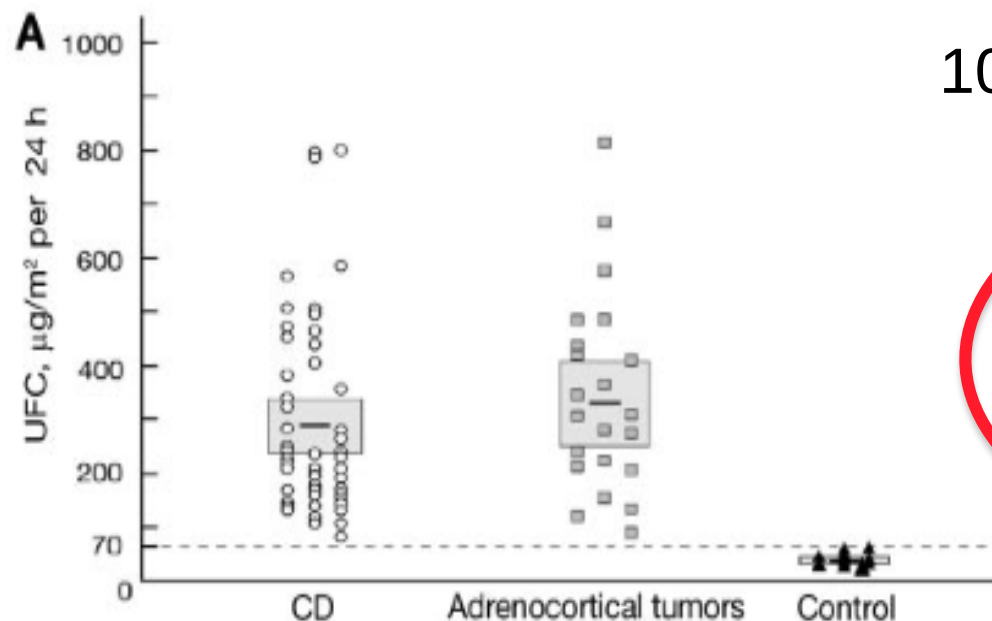
80 CD
4 AA
21 PPNAD
20 CONTROLLI

6% (5 of 80) CD
32% (8 of 25)
AICS

FN*

10% (2 of 20) controlli

FP*



sensibilità 88%
specificità 90%
PPV 98%

Batista 2007

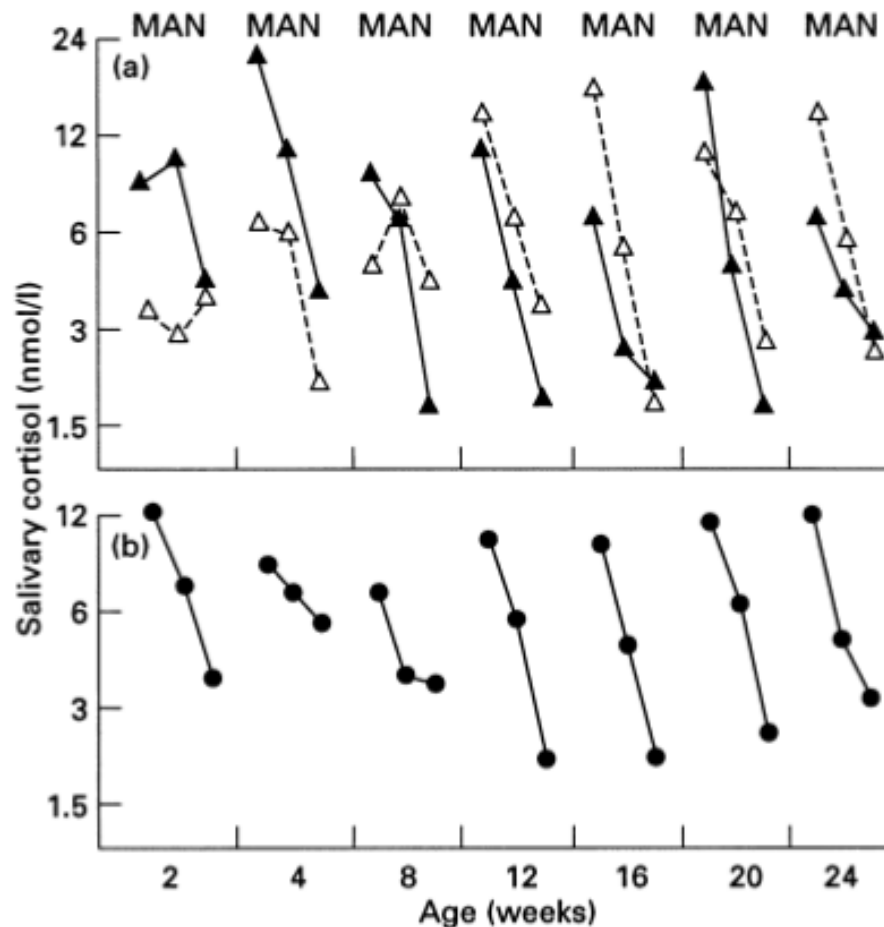
* Su almeno un campione su tre

Longitudinal evaluation of the development of salivary cortisol circadian rhythm in infancy

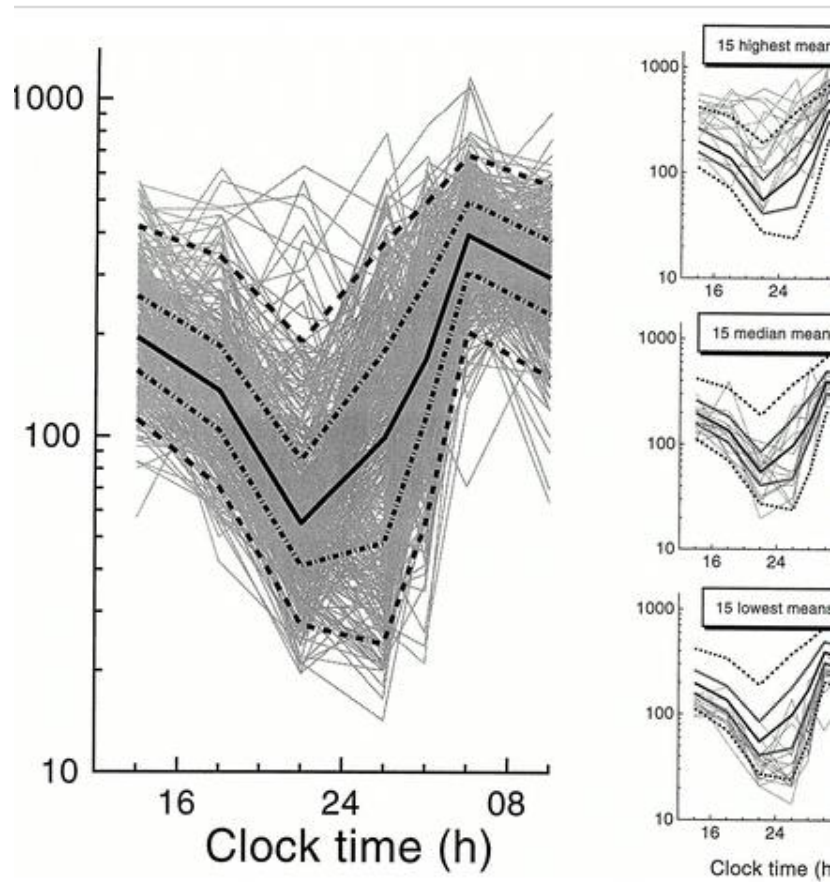
Development of salivary cortisol circadian rhythm in infancy.

a. Representative examples of individual development

B. mean concentrations for all subjects. M morning, A afternoon N night



Circadian Cortisol Rhythms in Healthy Boys and Girls: Relationship with Age, Growth, Body Composition, and Pubertal Development



All serum cortisol profiles for the boys and girls at all pubertal stages (*left panel*). Also indicated are the 5th, 25th, 50th, 75th, and the 95th percentiles.

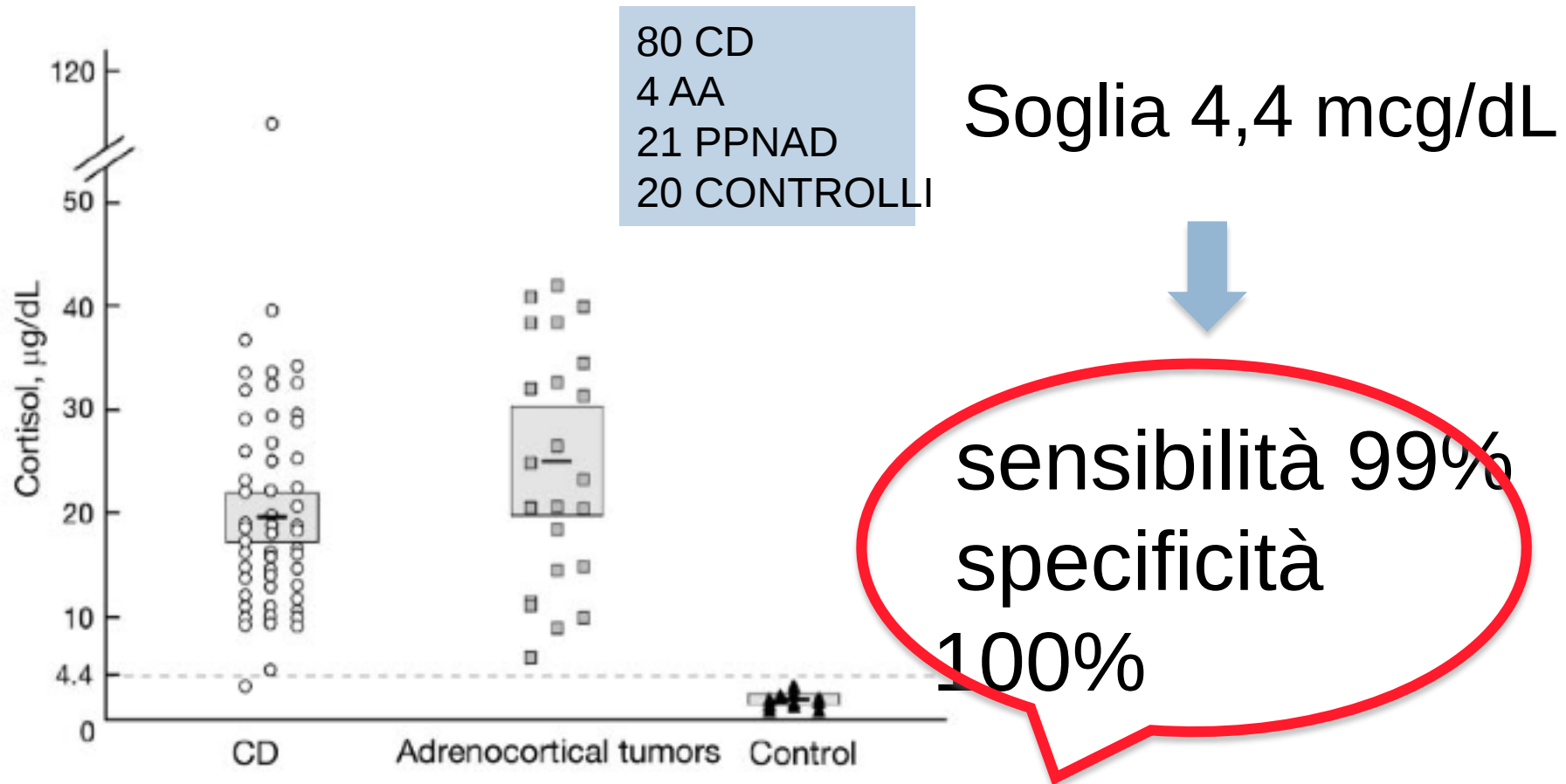
The *right panels* show the 15 lowest, 15 highest, and 15 median profiles.

Cushing's syndrome in children and adolescent: presentation, Diagnosis and Therapy

with Cushing's Syndrome.

VALUE*	CUSHING'S DISEASE	PRIMARY ADRENAL DISEASE	ECTOPIC CORTICOTROPIN SECRETION	NORMAL RANGE†
		<i>mean ±SD</i>		
24-Hr urinary cortisol ($\mu\text{g}/\text{m}^2/\text{day}$)	455 ± 563	462 ± 309	1142 ± 1514	20–70
24-Hr 17-OHCS (mg/g creatinine/day)	18 ± 9	16 ± 9	6 ± 0.8	2–7
Morning plasma cortisol ($\mu\text{g}/\text{dl}$)‡	18.9 ± 8.2	21.1 ± 6.6	41.4§	5–25
Evening plasma cortisol ($\mu\text{g}/\text{dl}$)¶	19.4 ± 7.5	27.5 ± 11.2	45.6§	<5
Base-line plasma corti- cotropin (pg/ml)	58 ± 6	6 ± 2	628 ± 362	5–26

Diagnostic Tests for Children Who Are Referred for the Investigation of Cushing Syndrome



Midnight cortisol values in children with CS (n = 80) and adrenocortical tumors (n = 25) and in control subjects (n = 20).

Batista 2007

TABLE 2 Sensitivities and Specificities of Biochemical Tests for Diagnosis of CS in Children in Our Study Using Previously Published Cutoff Values

Study	Value	Sensitivity, % (n/N)	Specificity, % (n/N)
Midnight cortisol^a			
Newell-Price et al ²⁷ (1995)	1.8 $\mu\text{g/dL}$ (50 nmol/L)	100 (105/105)	60 (12/20)
This study	4.4 $\mu\text{g/dL}$ (121 nmol/L)	99 (104/105)	100 (20/20)
Papanicolau et al ¹⁷ (1998)	7.5 $\mu\text{g/dL}$ (207 nmol/L)	97 (102/105)	100 (20/20)
Corticotropin^b			
Newell-Price et al ³⁵ (2006)	<5 pg/ml (1.1 pmol/L)	68 (17/25)	100 (80/80)
This study	29 pg/ml (6 pmol/L)	70 (56/80)	100 (25/25)
CRH test^b			
Nieman et al ¹⁸ (1993)	Cortisol increase 20%	74 (59/80)	
Nieman et al ¹⁸ (1993)	Corticotropin increase 35%	81 (64/79)	
HDDST^c			
This study	20%	97.5 (77/79)	100 (23/23)
Tyrell et al ³⁶ (1986)	50%	77 (61/79)	100 (23/23)
Dichek et al ¹⁹ (1994)	68%	75 (59/79)	100 (23/23)

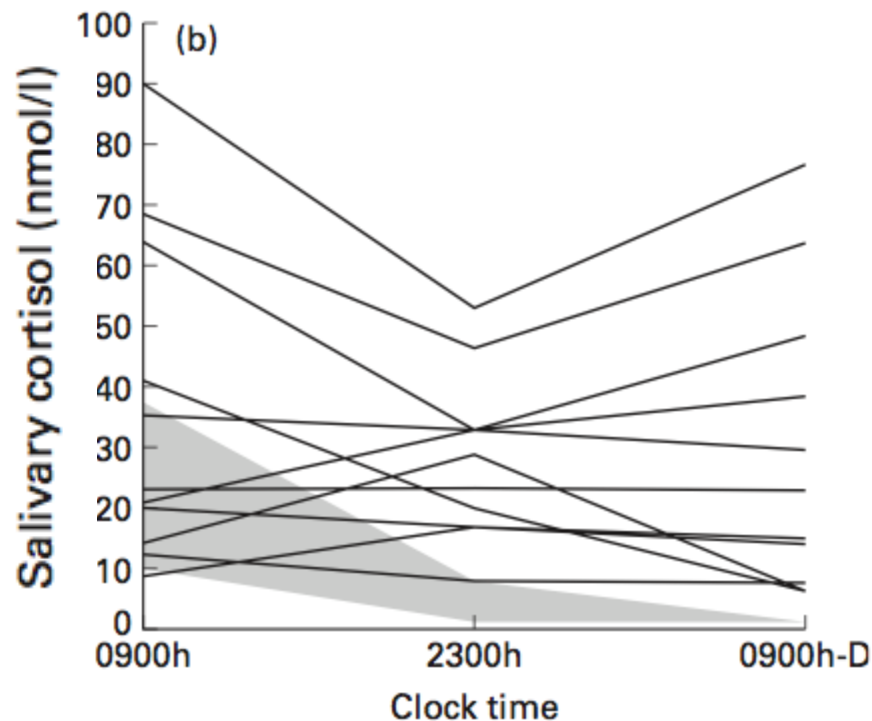
^a Different assays and methods to collect samples may have contributed to yield different results.

^b Corticotropin level was not available for 1 patient with CD.

^c HDDST results were not available for 1 patient with CD. Two children with adrenal disease did not undergo HDDST but underwent Liddle's test.

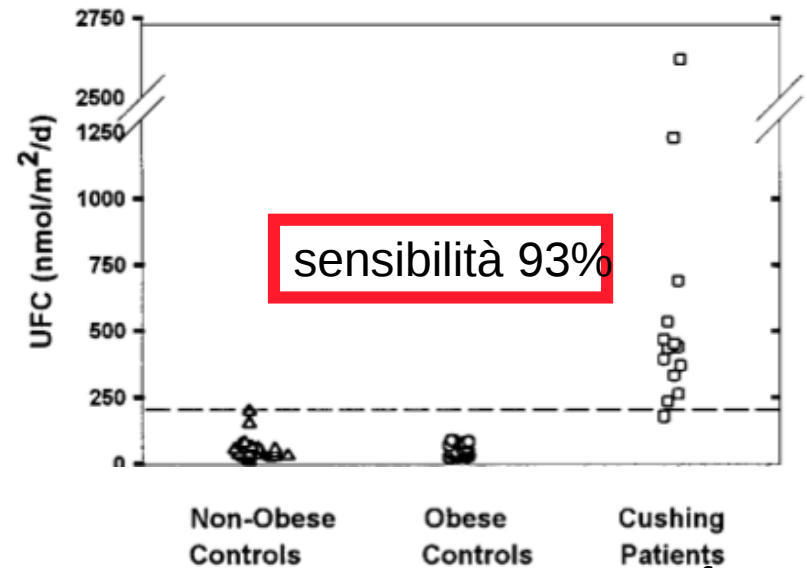
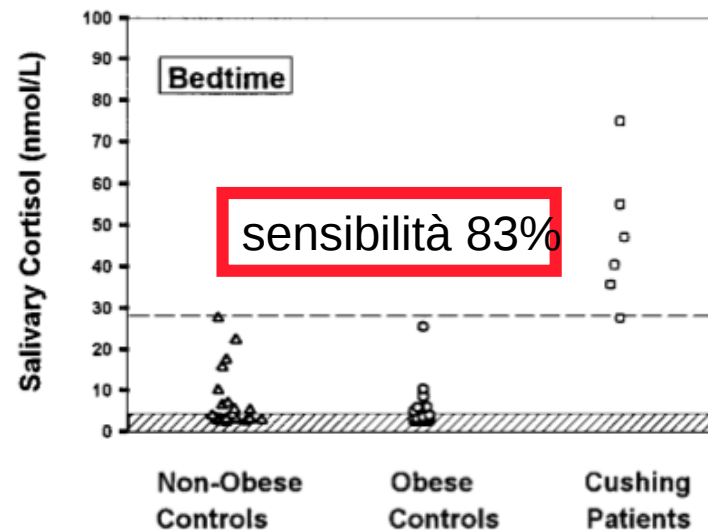
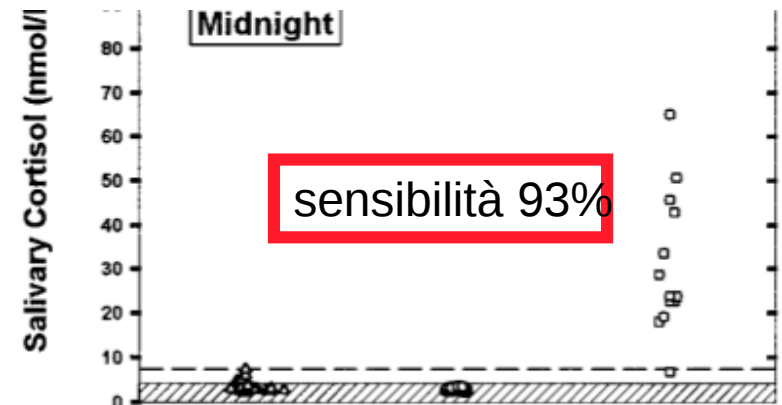
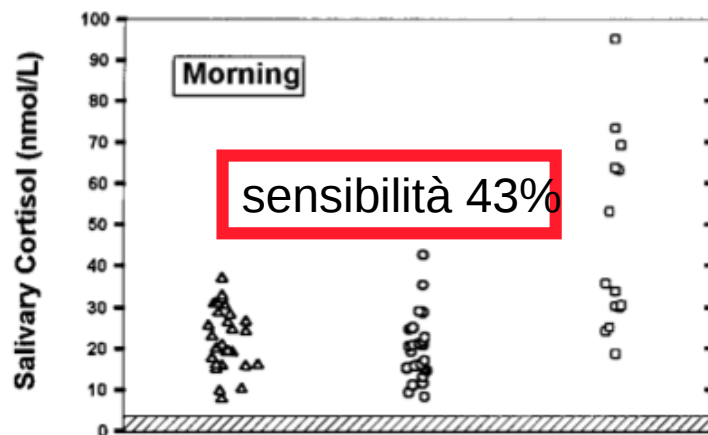
Salivary cortisol for screening of Cushing's syndrome in children

21 obese and 11 Cushing's syndrome children. Each line represents the data for an individual. The shaded area correspond to the 5th and 95th percentiles of obese children values.



sensibilità 100%
specificità 95,2%

Nighttime salivary cortisol measurement as a simple, noninvasive, outpatient screening test for Cushing's syndrome in children and adolescents



Test di soppressione overnight con desametasone a bassa dose

- 15mcg/kg desametasone
- Valore soglia di cortisolemia per adeguata soppressione < 3 mcg/dL
- Limitata specificità (15-20% falsi positivi)
- Non disponibilità di studi formali di valutazione della accuratezza in età pediatrica

Severe Obesity Confounds the Interpretation of Low-Dose Dexamethasone Test Combined with the Administration of Ovine Corticotrophin-Releasing Hormone in Childhood Cushing Syndrome

TABLE 5. Screening tests for CS in children

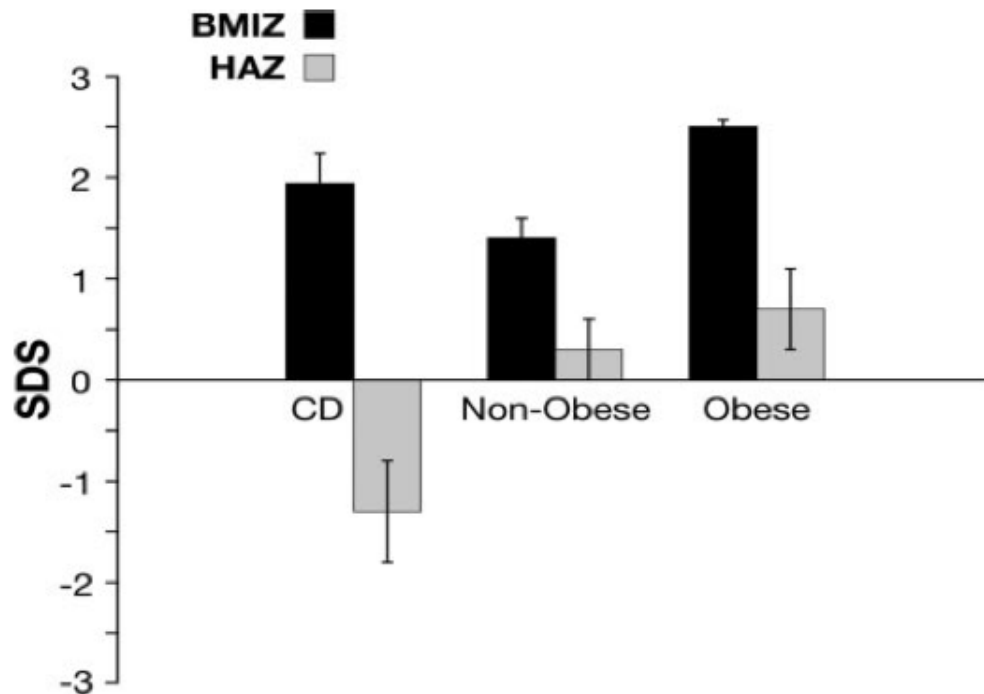
Screening test (Ref.)	Sensitivity (%)	Specificity (%)	Setting
UFC (25) ^a	88	80	Outpatient
Midnight cortisol (25)	99	100	Inpatient
Midnight salivary cortisol (9)	93	100	Outpatient
Salivary cortisol (23 h) (10)	100	95.2	Outpatient
Salivary cortisol after Dex (10)	100	95.2	Outpatient
Salivary cortisol (23 h) and after Dex (10)	100	100	Outpatient
LDDST-UFC (present study)	100	100	Outpatient
LDDST-serum cortisol (present study)			Outpatient
CD vs. nonobese children (1.4 $\mu\text{g}/\text{dl}$ or 38 nmol/liter)	91	100	
CD vs. obese children (1.4 $\mu\text{g}/\text{dl}$ or 38 nmol/liter)	91	91	
CD vs. obese and nonobese			
1.2 $\mu\text{g}/\text{dl}$ or 33 nmol/liter	91	95	
1.0 $\mu\text{g}/\text{dl}$ or 28 nmol/liter	100	0	
1 mg ODST (10, 30–33) ^b	82.5–100	87.5–95.2	Outpatient
Dex-oCRH test (present study)			Outpatient
CD vs. nonobese children (1.4 $\mu\text{g}/\text{dl}$ or 38 nmol/liter)	100	100	
CD vs. obese children (1.4 $\mu\text{g}/\text{dl}$ or 38 nmol/liter)	100	55	
CD vs. obese and nonobese			
3.2 $\mu\text{g}/\text{dl}$ or 88 nmol/liter	91	95	
2.2 $\mu\text{g}/\text{dl}$ or 61 nmol/liter	100	90.5	

Setting indicates which tests can be performed as outpatient or inpatient. ODST, Overnight Dex suppression.
a UFC collection sensitivity and specificity varies with the number of days of collection.

b Results are mostly in adult patients; reported values are for serum or salivary cortisol after 1 mg ODST.

Batista 2008

Severe Obesity Confounds the Interpretation of Low-Dose Dexamethasone Test Combined with the Administration of Ovine Corticotrophin-Releasing Hormone in Childhood Cushing Syndrome



Mean BMIZ scores and HAZ scores for patients in the study. Overall mean BMIZ score for pediatric patients with CD is usually above the mean, but the mean HAZ score is not. Data are presented as mean $\pm$ SEM. SDS, SD score.

Test di soppressione con desametasone a bassa dose (2 + 2 mg) per due giorni

- 30 mcg/kg desametasone per due giorni (dosi refratte) se peso < 40 Kg
- Valore soglia di cortisolemia per adeguata soppressione < 1,8 mcg/dL
- Non disponibilità di studi formali di valutazione della accuratezza in età pediatrica

Screening

Cortisolo notturno plasmatico $\leq 1,8$ mcg/dL / $\leq 4,4$ mcg/dL
salivare $\leq 0,27$ mcg/dL

Cortisolo libero urinario > 70 mcg/m²/24 ore

Cortisolo plasmatico ore 8 post DEXA overnight > 3 mcg/dL (?)

Cortisolo plasmatico ore 8 post DEXA 2 gg $\leq 1,8$ mcg/dL

Sindrome di Cushing



Screening

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Cortisolo libero urinario > 70 mcg/m²/24 ore

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Sindrome di Cushing



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Sindrome di Cushing



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Sindrome di Cushing



Screening

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Cortisolo plasmatico ore 8 post DEXA 2 gg $\leq 1,8$ mcg/dL

Sindrome di Cushing



Differenziazione forme ACTH dipendenti/indipendenti



ACTH plasmatico al mattino
HDDST overnight
HDDST 2 gg
LDDST (2 + 2 mg)

Screening

Cortisolo notturno plasmatico $\leq 1,8$ mcg/dL – $\leq 4,4$ mcg/dL
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Cortisolo plasmatico ore 8 post DEXA 2 gg $\leq 1,8$ mcg/dL

Sindrome di Cushing



Differenziazione forme ACTH dipendenti/indipendenti



ACTH plasmatico al mattino

Cushing's syndrome in children and adolescent: presentation, Diagnosis and Therapy

with Cushing's Syndrome.

VALUE*	CUSHING'S DISEASE	PRIMARY ADRENAL DISEASE	ECTOPIC CORTICOTROPIN SECRETION	NORMAL RANGE†
		<i>mean ±SD</i>		
24-Hr urinary cortisol ($\mu\text{g}/\text{m}^2/\text{day}$)	455 ± 563	462 ± 309	1142 ± 1514	20–70
24-Hr 17-OHCS (mg/g creatinine/day)	18 ± 9	16 ± 9	6 ± 0.8	2–7
Morning plasma cortisol ($\mu\text{g}/\text{dl}$)‡	18.9 ± 8.2	21.1 ± 6.6	41.4§	5–25
Evening plasma cortisol ($\mu\text{g}/\text{dl}$)	19.4 ± 7.5	27.5 ± 11.2	45.6§	<5
Base-line plasma corti- cotropin (pg/ml)	58 ± 6	6 ± 2	628 ± 362	5–26

Diagnostic Tests for Children Who Are Referred for the Investigation of Cushing Syndrome

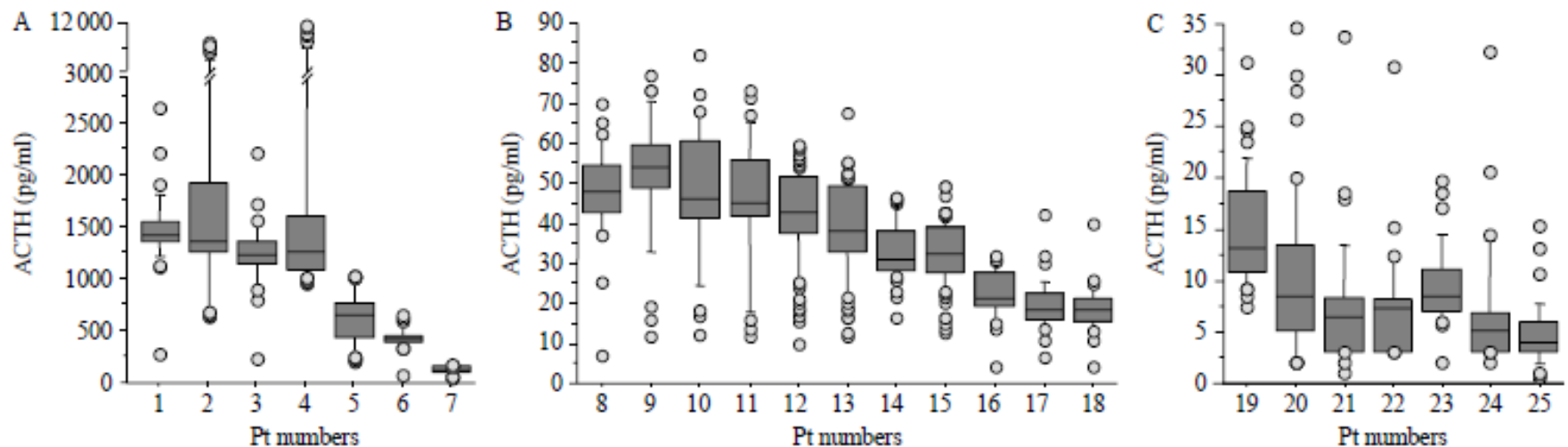
ACTH	
pg/ml	range
80 CD	} 1 - 29
4 AA	
21 PPNAD	
20 CONTROLLI	

Soglia 29 pg/ml



sensibilità 70%
specificità
100%

Assessment of ACTH assay variability: a multicenter study



Centile distribution of ACTH concentrations in each patient. Box depicts median, 25° and 75° percentile; 10° and 90° percentile as S.E.M. and values outside 10° and 90° are shown as dots. Panel A: results in patients with high ACTH secretion; Panel B: results in patients with normal ACTH secretion; Panel C: results in patients with suppressed ACTH secretion.

Screening

Cortisolo notturno plasmatico $\leq 1,8$ mcg/dL – $\leq 4,4$ mcg/dL
salivare $\leq 0,27$ mcg/dL

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Cortisolo plasmatico ore 8 post DEXA 2 gg $\leq 1,8$ mcg/dL

Sindrome di Cushing



Differenziazione forme ACTH dipendenti/indipendenti



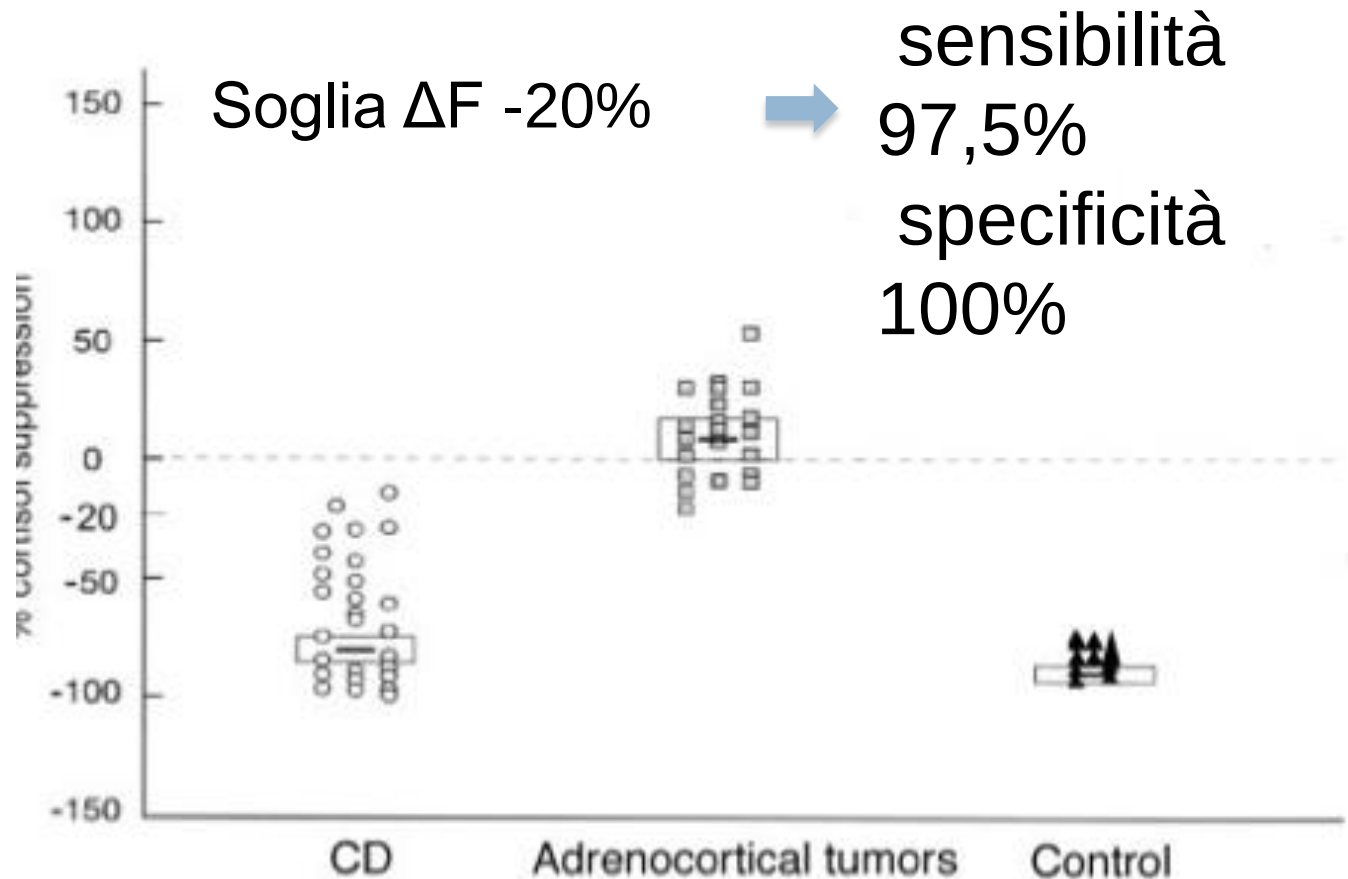
HDDST overnight
HDDST 2 gg
LDDST (2 + 2 mg)

H
D
D
S
T

		<i>soglia</i> <i>inibizione</i>	<i>sensibilità</i>	<i>specificità</i>
dexa 8+8 po	17OHCS	≥ 50%		
	F	≥ 50%		
	17OHCS	≥ 64%	83%	100%
	UFC	≥ 90%		
	17OHCS	≥ 69%	79%	100%
DEXA 8 mg on	F	≥ 50%	77-92%	57-100%
		≥ 68%	71%	100%
		≥ 20%	97%	100%
DEXA 5 mg ev	F	≥ 50%		
DEXA 7 mg ev	F	▲ 7 mcg	100%	90%

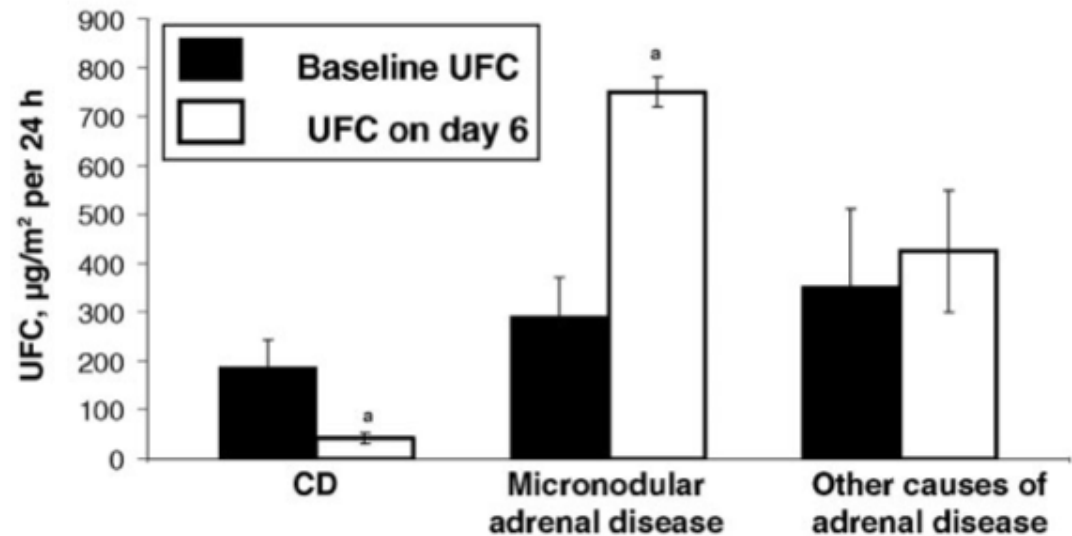
Diagnostic Tests for Children Who Are Referred for the Investigation of Cushing Syndrome

Cortisol response to an overnight HDDST in patients with CD ($n = 79$) and adrenocortical tumors ($n = 23$) and in control subjects ($n = 20$). For 1 patient with CD, HDDST test results were not available. Two children with adrenal disease did not undergo HDDST but underwent Liddle's test. Significant overlap occurred between individual points.



Diagnostic Tests for Children Who Are Referred for the Investigation of Cushing Syndrome

Mean change in 24-hour excretion of UFC during the Liddle's test. Filled bars represent baseline UFC excretion values, the mean of 2 days of 24-hour urine collection (day 1 and day 2 of the Liddle's test). Open bars represent UFC on day 6 of the Liddle's test. For children with CD ($n = 12$), 24-hour UFC excretion decreased on day 6 of the Liddle's test. For children with micronodular adrenal disease (primary pigmented nodular adrenocortical lesions) ($n = 16$), 24-hour UFC excretion increased significantly on day 6 of the Liddle's test. Children with other causes of adrenal disease (unilateral adenomas and macronodular adrenal disease) ($n = 4$) had a modest increase in their 24-hour UFC excretion on day 6 of the Liddle's test. Error bars represent the SE. $a P < .05$, baseline 24-hour UFC excretion compared with UFC on day 6.



Screening

Cortisolo notturno plasmatico $\leq 1,8$ mcg/dL – $\leq 4,4$ mcg/dL
salivare $\leq 0,27$ mcg/dL

Cortisolo libero urinario > 70 mcg/m²/24 ore

Cortisolo plasmatico ore 8 post DEXA overnight > 3 mcg/dL (?)

Cortisolo plasmatico ore 8 post DEXA 2 gg $\leq 1,8$ mcg/dL

Sindrome di Cushing



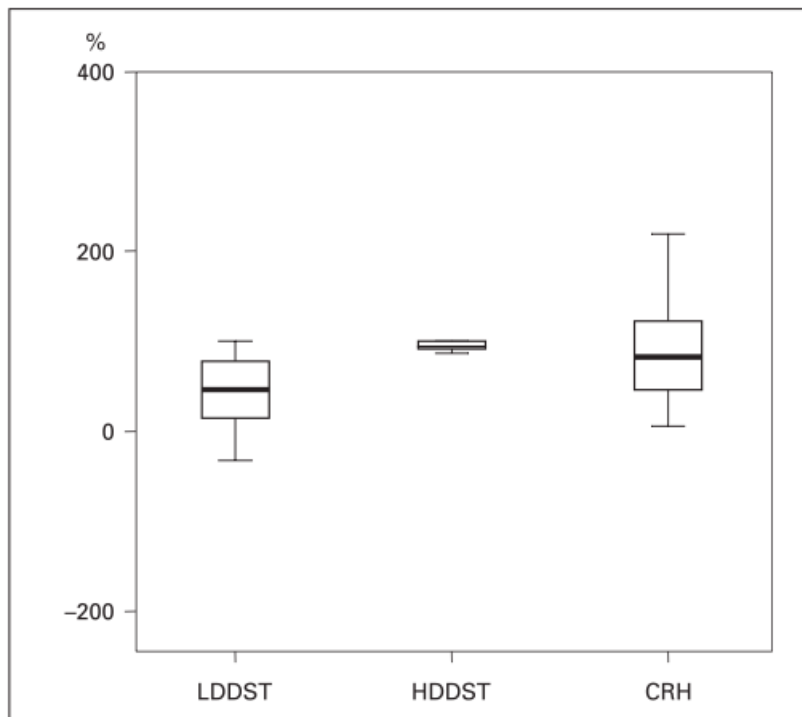
Differenziazione forme ACTH dipendenti/indipendenti



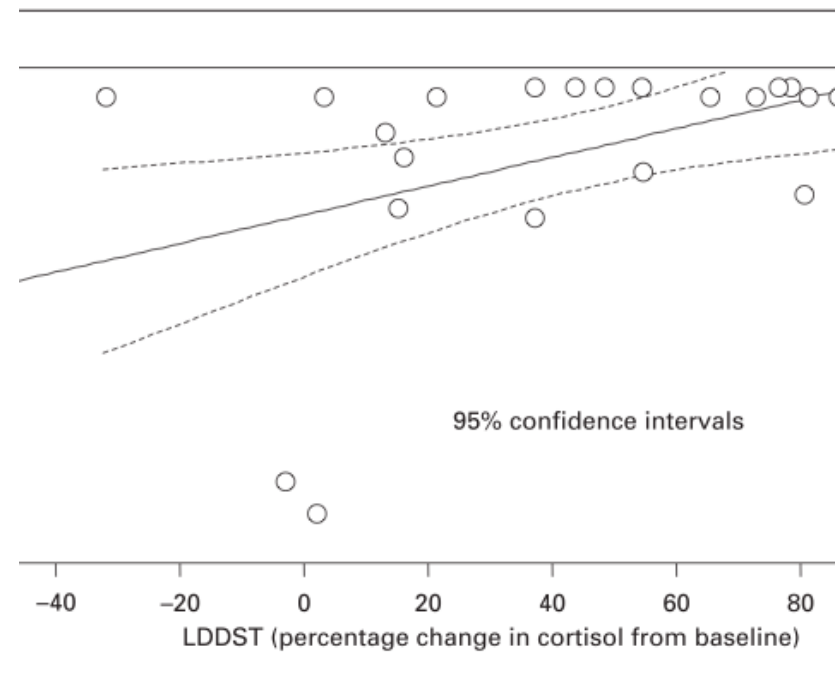
LDDST (2 + 2 mg)

The Discriminatory Value of the Low-Dose Dexamethasone Suppression Test in the Investigation of Paediatric Cushing's Syndrome

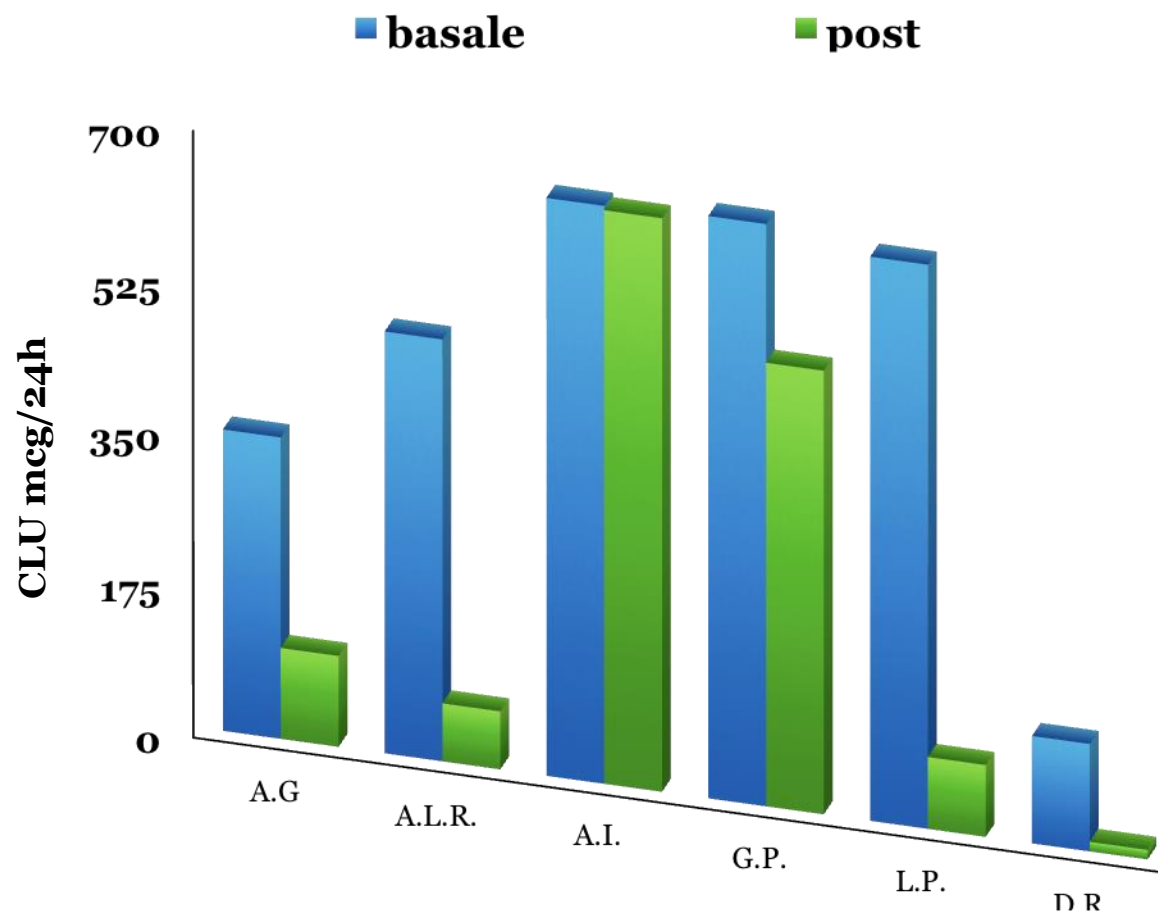
Percentage change from baseline of serum cortisol (mean $\pm$ SD and range) during LDDST and HDDST and the CRH test in 24 patients with CD



Correlation between the percentage change serum cortisol from baseline during the LDDST and HDDST in 24 patients with CD ($r = +0.45$, $p \neq 0.05$).



Test con desametasone (2 mg per 2 giorni)



Screening

Cortisolo notturno plasmatico $\leq 1,8$ mcg/dL – $\leq 4,4$ mcg/dL
salivare $\leq 0,27$ mcg/dL
Cortisolo libero urinario > 70 mcg/m²/24 ore
Cortisolo plasmatico ore 8 post DEXA overnight > 3 mcg/dL (?)
Cortisolo plasmatico ore 8 post DEXA 2 gg $\leq 1,8$ mcg/dL

Sindrome di Cushing



Differenziazione forme ACTH dipendenti/indipendenti



ACTH plasmatico al mattino
HDDST overnight
HDDST 2 gg
LDDST (2 + 2 mg)



ACTH indipendenti



Imaging
Liddle test

a.b. 13 anni

H 155 cm, Kg 48

Padre 175 cm, madre 160 cm
importante rallentamento della
crescita negli ultimi due anni
(centile al 50° centile circa).

Test ITT GH picco 0,2 ng/mL,
ng/ml

Test clonidina GH picco 9,8 ng/mL

Rx mano sin: età ossea = età cronologica

Incremento ponderale negli ultimi due
anni

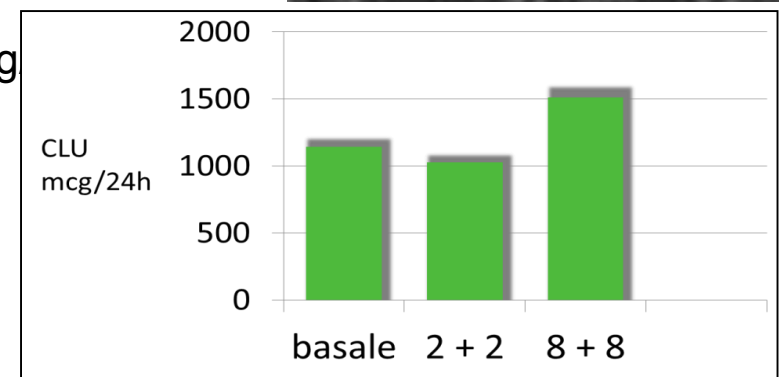
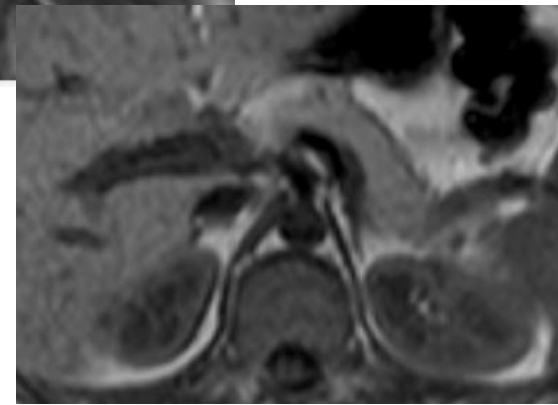
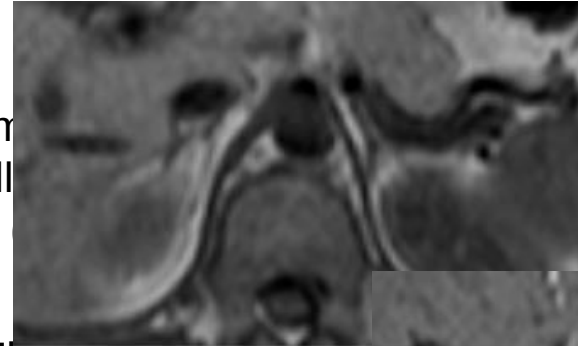
ore 8 pl Cortisolo 231 ug/L

ipertensione (MAP)

ore 24 pl Cortisolo 219 ug/L

24hU-Cortisolo 505 / 979/1027 µg

pl ACTH < 3 pg/ml



Screening

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salivare $\leq 0,27$ mcg/dL
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Sindrome di Cushing



Differenziazione forme ACTH dipendenti/indipendenti



ACTH plasmatico al mattino
HDDST overnight
HDDST 2 gg
LDDST (2 + 2 mg)

ACTH dipendenti

ACTH indipendenti



CRH test
Imaging
BIPSS



Imaging
Liddle test

Screening

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Sindrome di Cushing



Differenziazione forme ACTH dipendenti/indipendenti



ACTH plasmatico al mattino
HDDST overnight
HDDST 2 gg
LDDST (2 + 2 mg)

ACTH dipendenti

ACTH indipendenti



CRH test

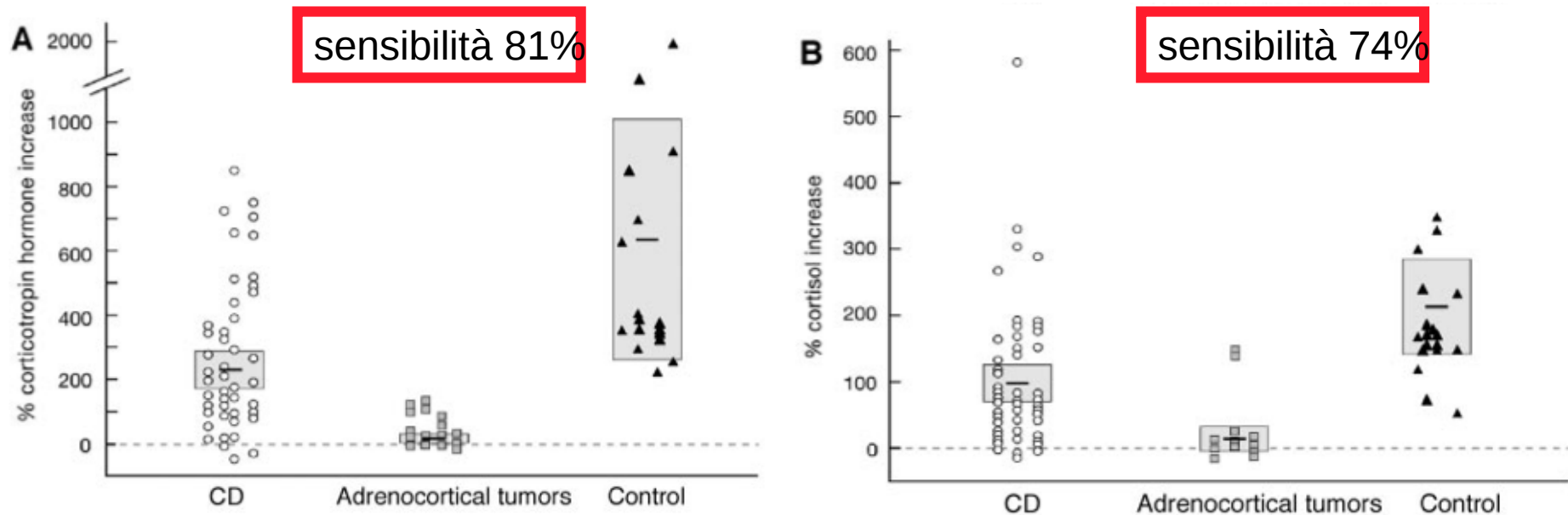


Imaging
Liddle test

CRH test

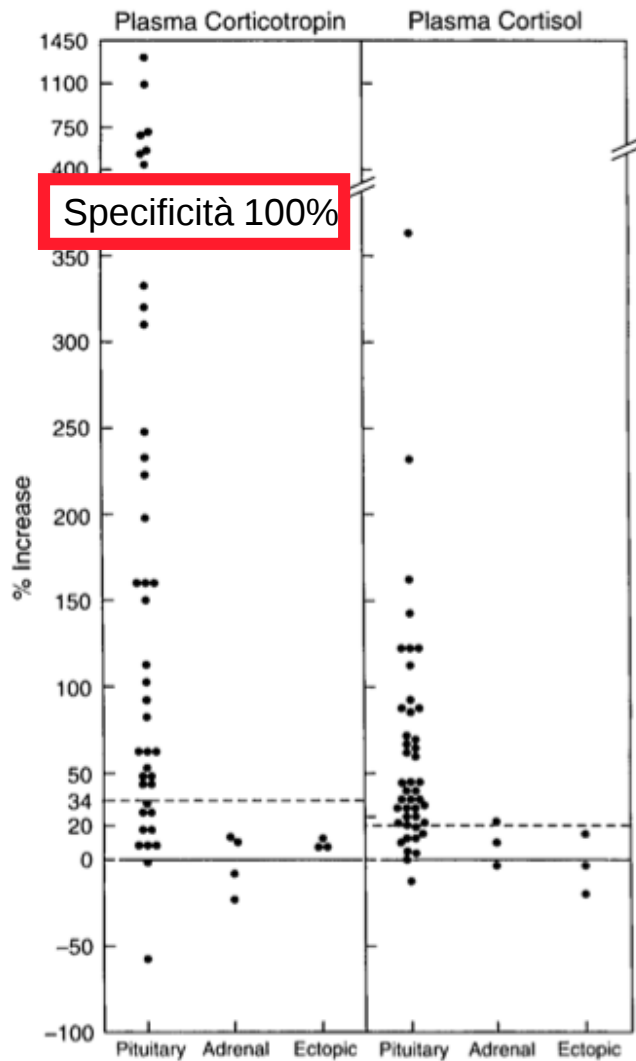
				<i>soglia stimolazione</i>	<i>sensibilità</i>	<i>specificità</i>
Kaye Crapo 1999		ACTH		$\geq 50\%$	86%	95%
		F		$\geq 20\%$	91%	95%
Nieman 1993		ACTH		$\geq 35\%$	93%	100%
		F		$\geq 20\%$	91%	88%

Diagnostic Tests for Children Who Are Referred for the Investigation of Cushing Syndrome



Corticotropin (A) and cortisol (B) responses to oCRH test in children with CD (n = 80), adrenocortical tumors (n = 25), and Control subjects (n = 20). CRH corticotropin level was not available for 1 patient with CD. Significant overlap occurred between individual points.

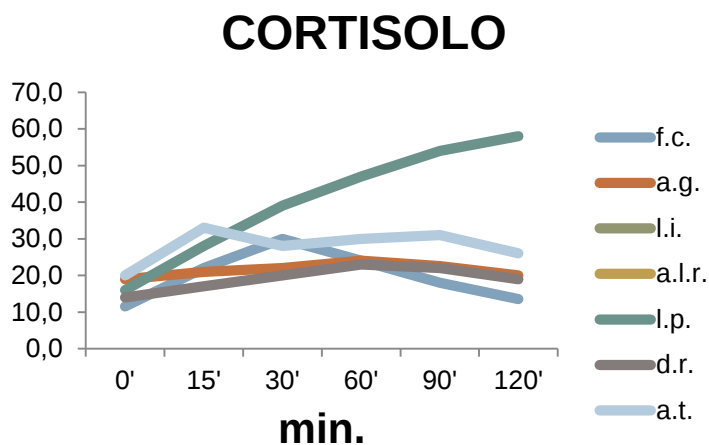
Cushing's syndrome in children and adolescent: presentation, Diagnosis and Therapy



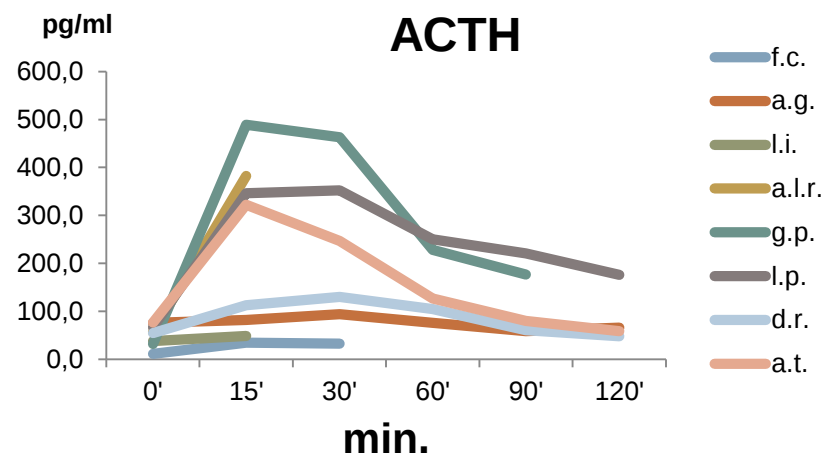
Increase in plasma corticotropin and cortisol concentrations above the means of the baseline values after CRH administration in 51 children and adolescent with pituitary adenomas, primary adrenal disease or ectopic corticotropin secretion

CRH TEST serie pediatrica di Niguarda

sensibilità 88%



sensibilità 78%



Screening

Cortisolo notturno plasmatico $\leq 1,8$ mcg/dL – $\leq 4,4$ mcg/dL
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Cortisolo libero urinario > 70 mcg/m²/24 ore
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Sindrome di Cushing



Differenziazione forme ACTH dipendenti/indipendenti



ACTH plasmatico al mattino
HDDST overnight
HDDST 2 gg
LDDST (2 + 2 mg)

ACTH dipendenti

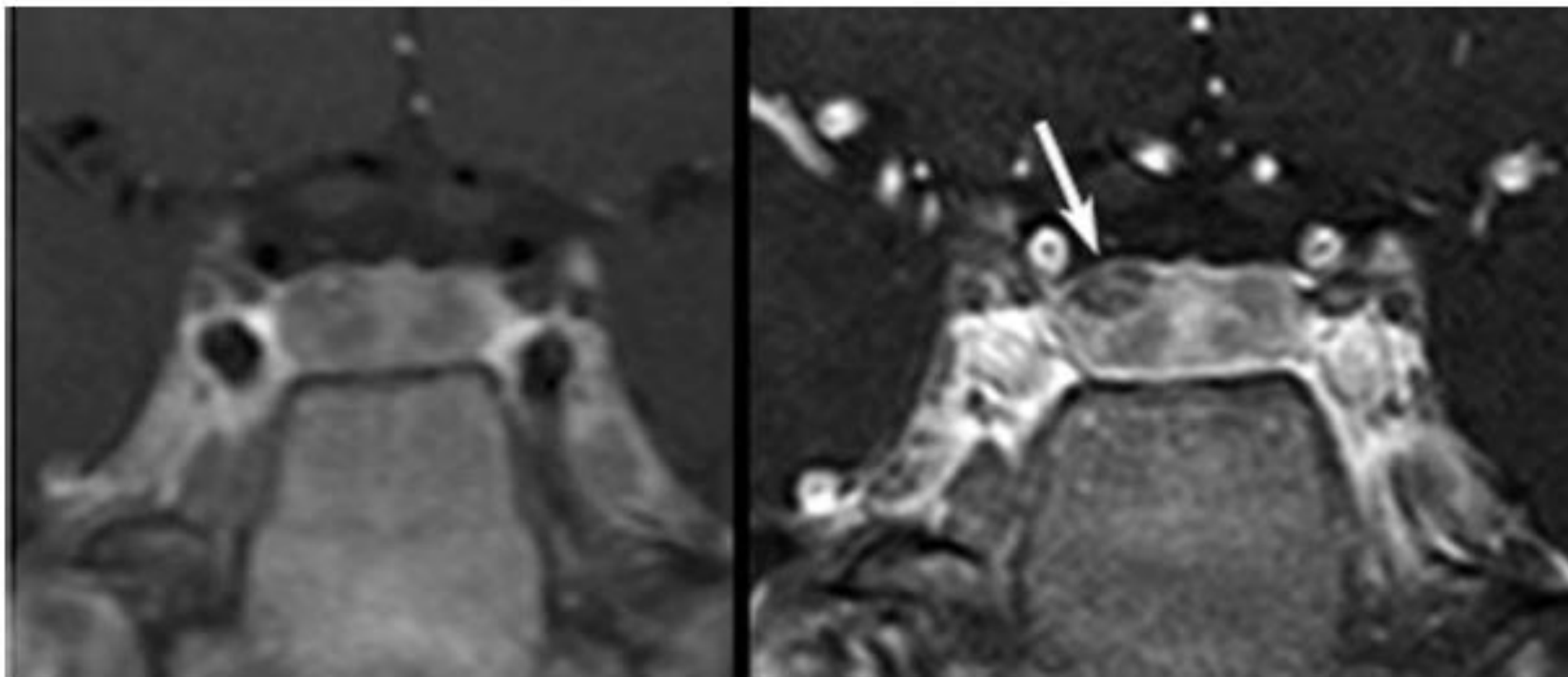


Imaging

ACTH indipendenti



Imaging
Liddle test



Pituitary MRI obtained after contrast with standard spin echo (left panel) and SPGR (right panel) techniques. Note microadenoma on the right side of the gland at the top of the anterior lobe seen with the SPGR, but not with the spin echo scan.

Size of adenomas, as measured at surgery, in patients with positive and negative MRI



	<i>Localizzazione dell'adenoma rispetto alla chirurgia</i>		
		con MRI (n. casi)	con CT (n. casi)
Dyer 1994		62% (40%) (8)	26% (60%) (27)
Magiakou 1994 *		52% (50)	
Knappe 1996		48% (70%) (42)	22% (27)
Massoud 1997		33% (12)	
Devoe 1997		72% (69%) (18)	23% (22)
Lienhardt 2001 **		45% (9%) (11)	
Kanter 2005		67% (82%) (33)	
Batista 2006 *		39% (94)	
Storr 2011 **		55% (34%) (38)	
Lonser 2013 *		50% (92%) (193)	
Niguarda 2013		55% (11)	

Comparisons in the epidemiology, diagnostic features and cure rate by transsphenoidal surgery between paediatric and adult-onset Cushing's diseases

	Macroadenomas on MR/CT image (<i>n</i> (%))	Microadenomas on MR image (<i>n</i> (%))	Concordance of image with surgery (%)
Paediatric patients	1/41 (2)	21/38 (55)	13/38 (34)
Adult patients	28/183 (15)	50/66 (76)	27/47 (57)
<i>P</i> value	0.045	0.03	0.058

Pituitary MRI and concordance with the surgical findings in paediatric and adult-onset CD.

Storr 2011

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Sindrome di Cushing



Differenziazione forme ACTH dipendenti/indipendenti



ACTH plasmatico al mattino
HDDST overnight
HDDST 2 gg
LDDST (2 + 2 mg)

ACTH dipendenti

ACTH indipendenti



BIPSS



Imaging
Liddle test

Cateterismo dei seni petrosi inferiori

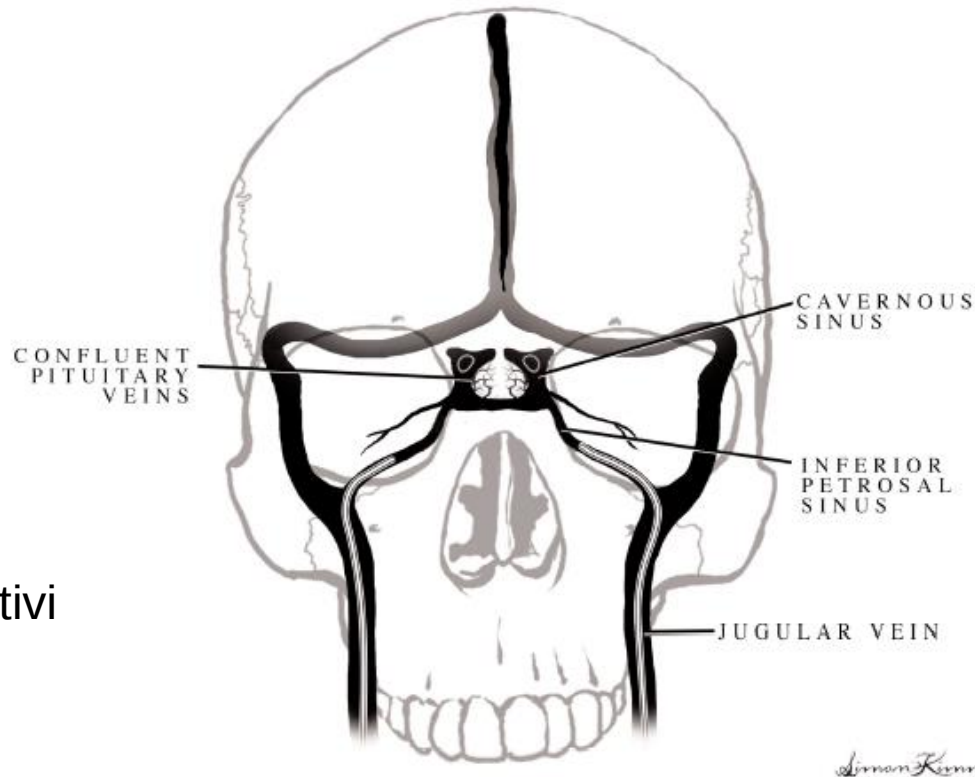


Fig. 1. Cerebral venous anatomy for IPSS.

Modalità
Criteri Interpretativi
Specificità
sensibilità

	<i>Localizzazione dell'adenoma rispetto alla chirurgia</i>		
	con BIPSS (n. casi)	con MRI (n. casi)	con CT (n. casi)
Dyer 1994		62% (40%) (8)	26% (60%) (27)
Magiakou 1994 *	76% (43)	52% (50)	
Knappe 1996	54% (13)	48% (70%) (42)	22% (27)
Massoud 1997	50% (4)	33% (12)	
Devoe 1997		72% (69%) (18)	23% (22)
Lienhardt 2001 **	91% (11)	45% (9%) (11)	
Kanter 2005	100% (7)	67% (82%) (33)	
Batista 2006 *	58% (94)	39% (94)	
Storr 2011 **	82% (29)	55% (34%) (38)	
Lonser 2013 *	72% (140)	50% (92%) (193)	
Niguarda 2013	60% (7)	55% (11)	

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Sindrome di Cushing



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ACTH plasmatico al mattino

HDDST overnight

HDDST 2 gg

LDDST (2 + 2 mg)

ACTH dipendenti

ACTH indipendenti



CRH test
Imaging
BIPSS



Imaging
Liddle test

Grazie per l'attenzione!

