CUSHING SYNDROME

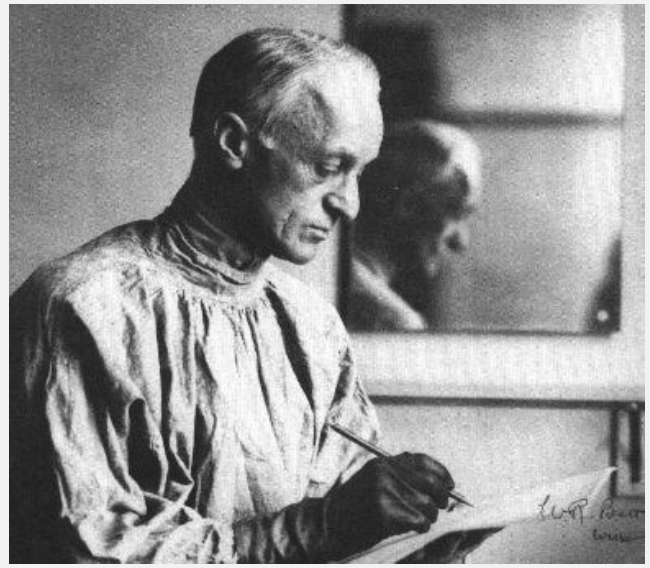
Beata Pyrżak

Pediatric and Endocrinology Department

Medical Univeristy of Warsaw

CUSHING'S SYNDROME

Cushing's syndrome is a multisystem disorder resulting from the body's prolonged exposure to excess glucocorticoids.



- The overall incidence of Cushing syndrome is approximately 2 to 5 new cases per million people per year. Only approximately 10% of the new cases each year occur in children.
- The most common cause of Cushing syndrome in children is exogenous or iatrogenic Cushing syndrome. This is the result of chronic administration of glucocorticoids or ACTH.

Regulation of Cortisol Secretion

1. Cortiocotropin-releasing hormone (CRH) is released from hypothalamic neurons in response to stress or low blood glucose and passes, by way of the hypothalamohypophyseal portal system, to the anterior pituitary.
2. CRH stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary.
3. ACTH stimulates the secretion of cortisol from the adrenal cortex.
4. Cortisol acts on target tissues, resulting in increased fat and protein breakdown, increased glucose levels, and anti-inflammatory effects.
5. Cortisol has a negative-feedback effect because it inhibits CRH release from the hypothalamus and ACTH secretion from the anterior pituitary.

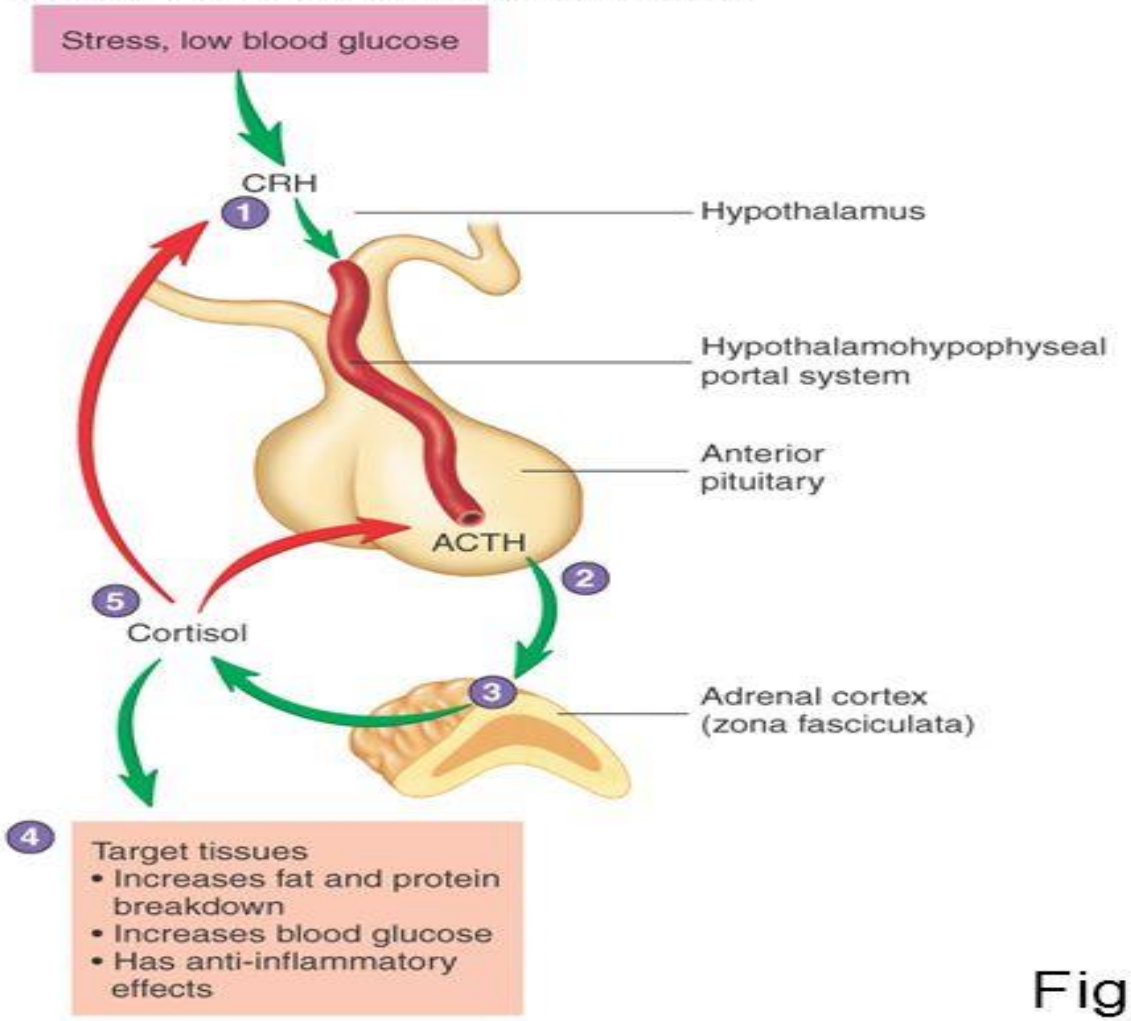
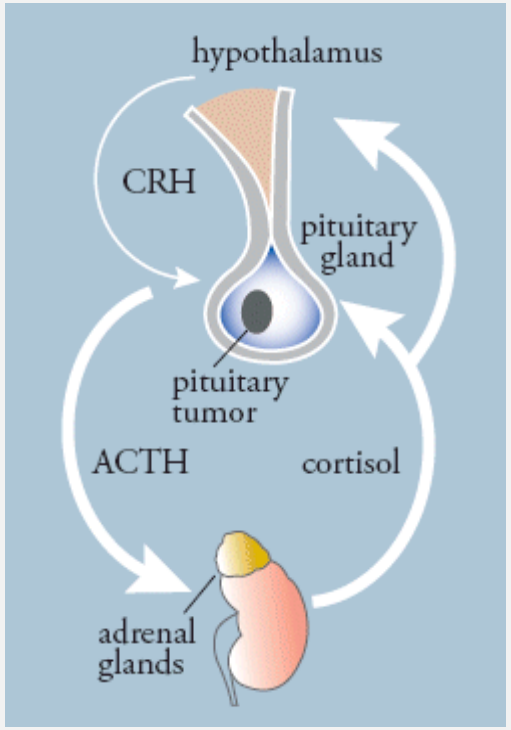
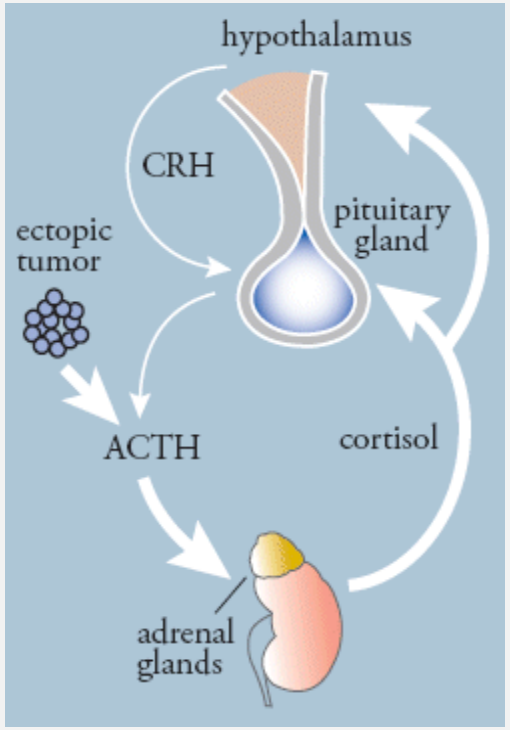
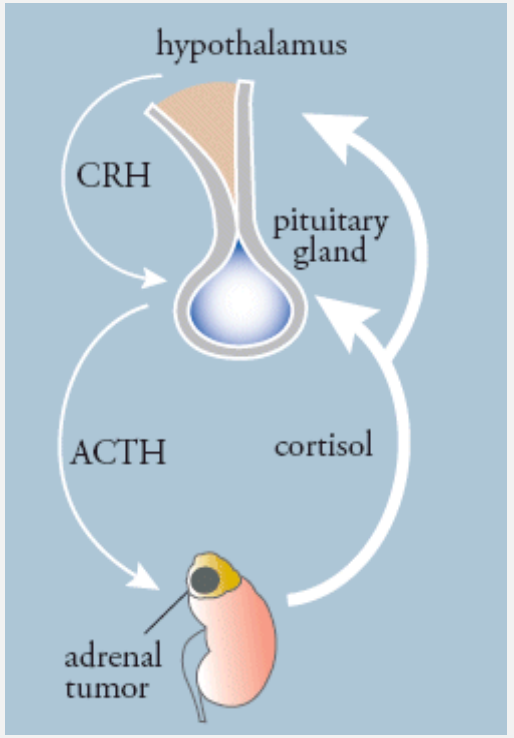


Fig. 15.24

Etiology of hypercortisolism







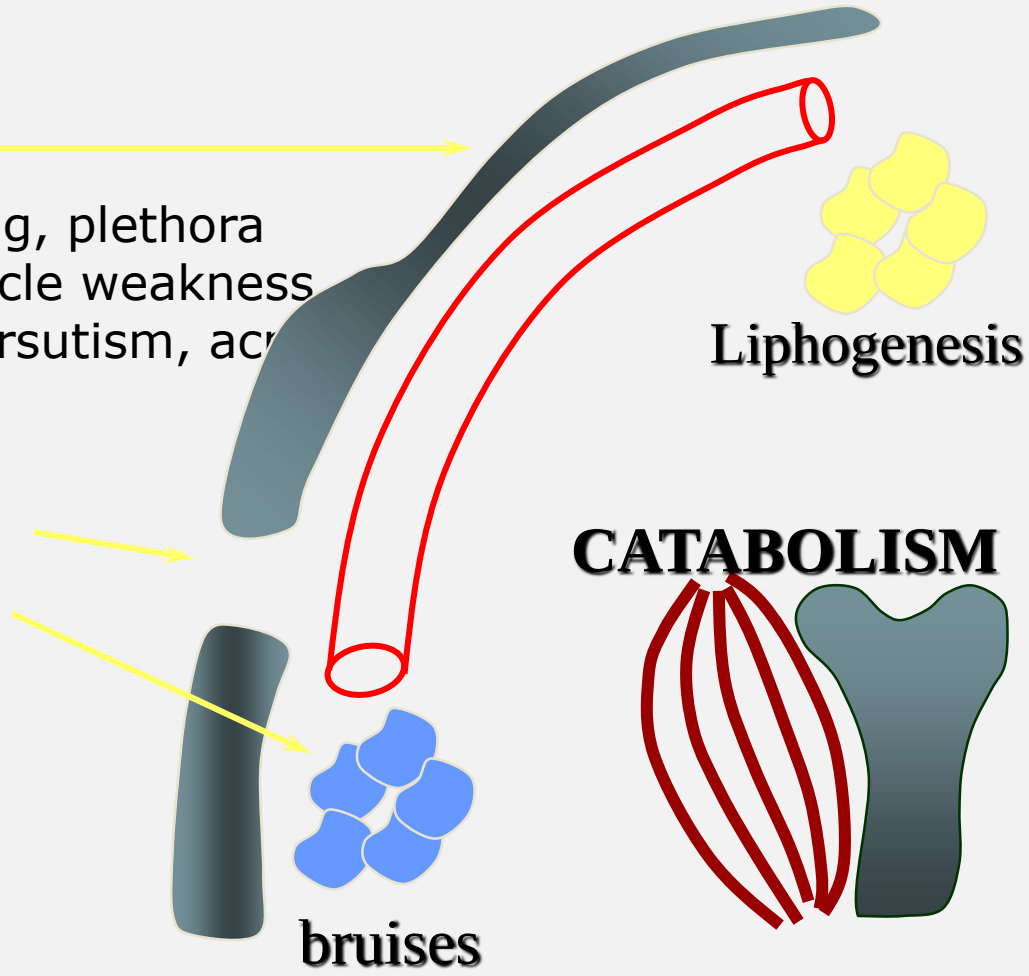
ACTH - **independent**

ACTH-dependent

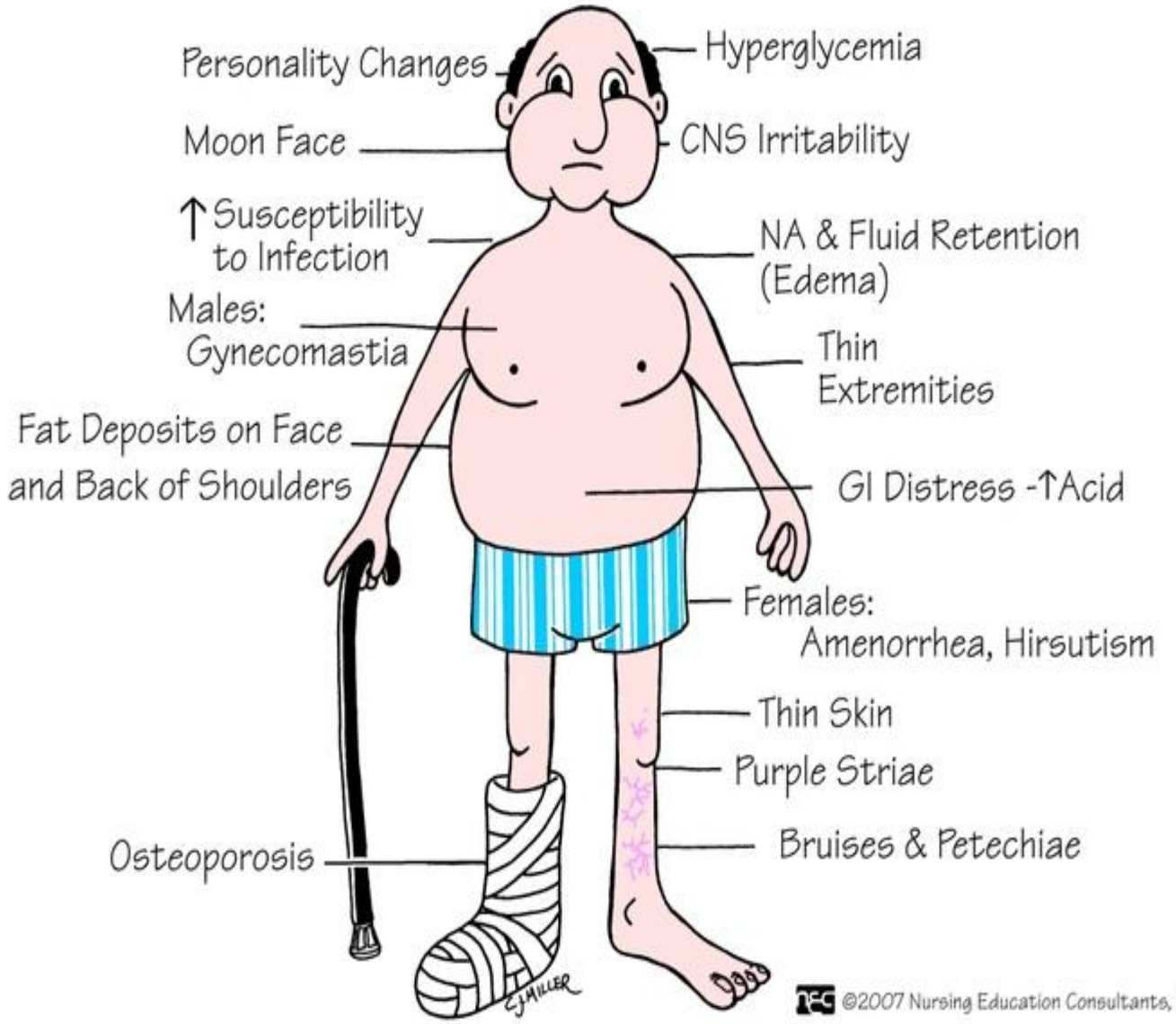
Cushing's disease

atrophy of the epidermis, thinning, plethora
oseopenia, striae, proximal muscle weakness
moon facies, easy bruisability, hirsutism, acr
osteopenia, etc

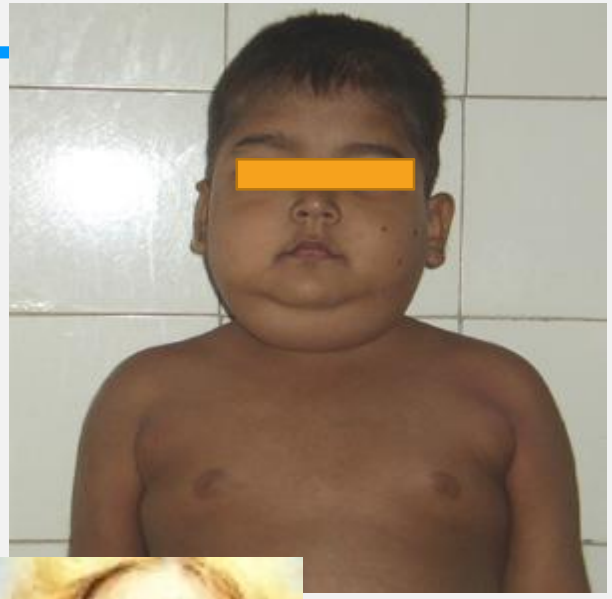
Because of hipercortisolism

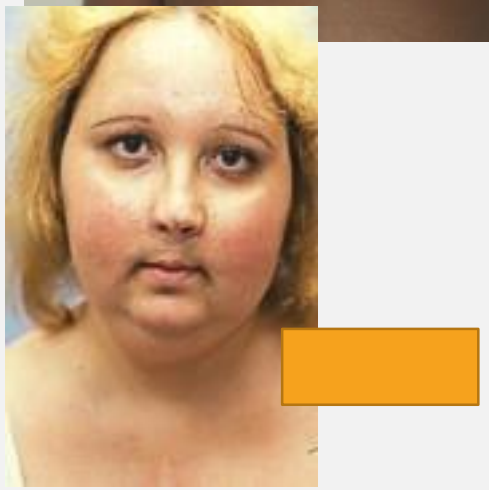


CUSHING'S SYNDROME



Cushing's disease





Cushing's disease presents with the signs and symptoms of hypercortisolism and androgen excess. The onset of these features is ussualy insidius, developing over months or years

- Growth retardation
- obesity (central fat distribution) ,
- hypertension,
- glucose intolerance,
- gonadal dysfunction are common features.

CLINICAL PRESENTATION IN CHILDREN

The most common presenting symptom:

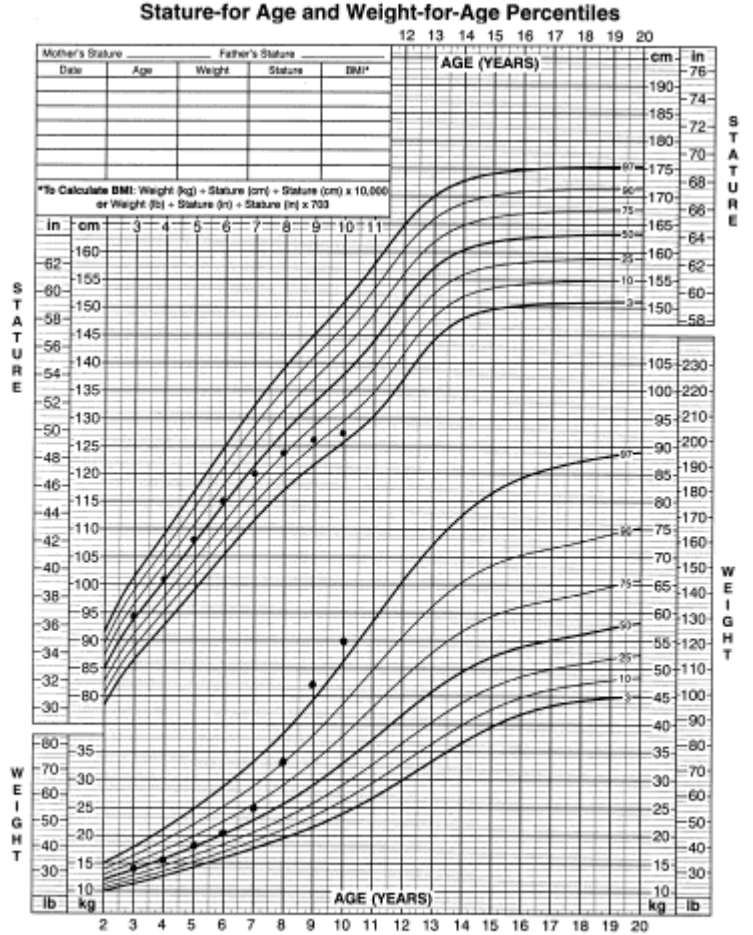
Weight gain; in childhood, lack of height gain

- ✓ **facial plethora**
- ✓ **headaches**
- ✓ **hypertension**
- ✓ **hirsutism**
- ✓ **amenorrhea, and delayed sexual development**
- ✓ **pubertal children may present with virilization**

Skin manifestations :

- ✓ **acne**
- ✓ **violaceous striae**
- ✓ **acanthosis nigricans**
- ✓ **easy bruisability**

Compared with adult patients with Cushing syndrome, symptoms that are less commonly seen in children include sleep disruption, muscular weakness, problems with memory, psychologic disturbances,



This is a growth chart that shows a decrease in height velocity at the same time there was an increase in weight velocity, which started at about 7 years of age.

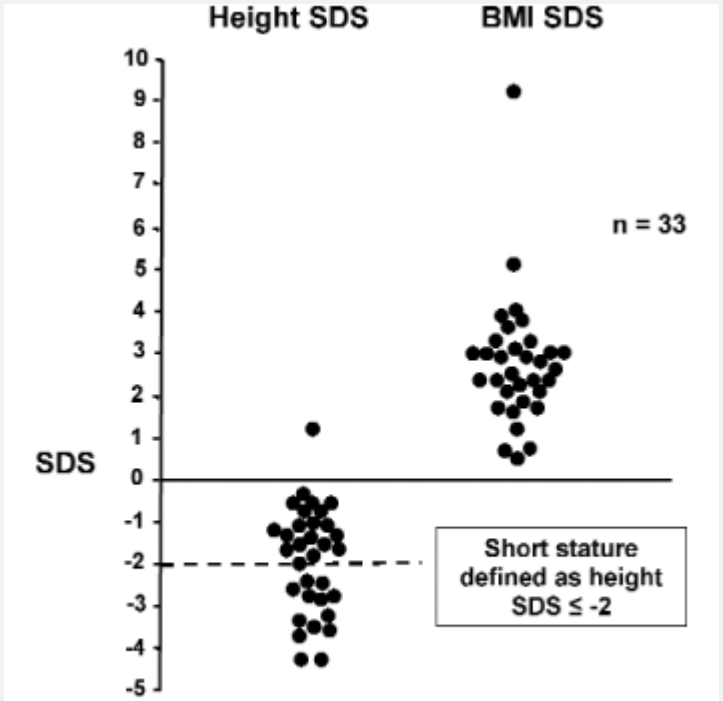


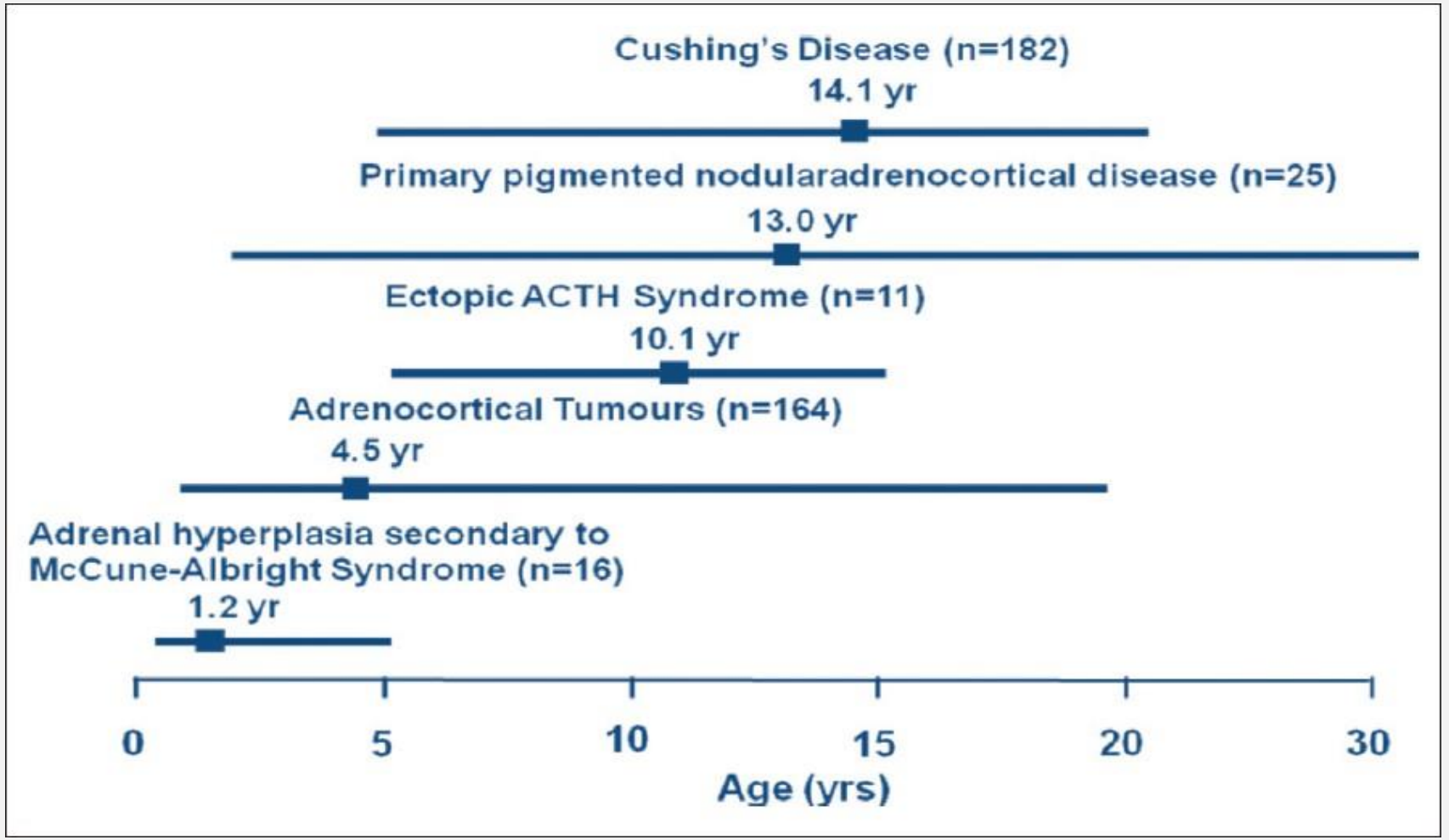
Figure 4. Height SDS and BMI SDS in 33 patients with CD. Short stature defined as Height SDS ≤ -2 is shown as a dotted line.

A typical growth chart for a child with Cushing syndrome

Pediatric Cushing's Disease: Management Issues
Martin O. Savage, Helen L. Storr

Indian Journal of Endocrinology and Metabolism

Indian Journal of Endocrinology and Metabolism



Pediatric Cushing's Syndrome
Chan et al. Arq Bras Endocrinol Metab 2007;51/8

CUSHING DISEASE

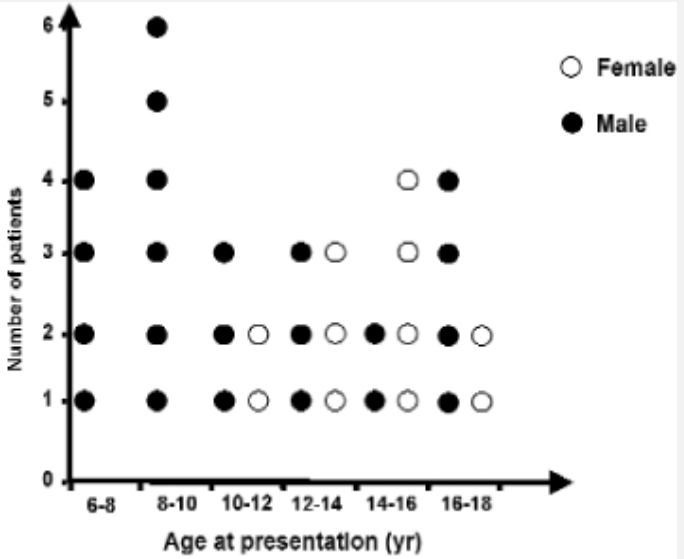


Figure 3. Preponderance of prepubertal male patients in pediatric CD as illustrated in our own case series (n = 33).

Cushing's disease is a primary pituitary disorder

(high frequency of pituitary adenomas), and that hypothalamic abnormalities are secondary to hypercortisolism

- It is usually caused by an ACTH-secreting pituitary microadenoma and, rarely, a macroadenoma.
- Cushing disease accounts for approximately 75% of all cases of Cushing syndrome in children over 7 years.

CUSHING DISEASE

- Ectopic ACTH production occurs rarely in young children; it also accounts for less than 1% of the cases of Cushing syndrome in adolescents. Sources of ectopic ACTH include small cell carcinoma of the lung, carcinoid tumors in the bronchus, pancreas, or thymus; medullary carcinomas of the thyroid, pheochromocytomas; and other neuroendocrinetumors, especially those of the pancreas and gut carcinoids.
- Rarely ACTH overproduction by the pituitary may be the result of CRH oversecretion by the hypothalamus or by an ectopic CRH source. However, this cause of Cushing syndrome has only been described in a small number of cases.

ACTH- INDEPENDENT CUSHING SYNDROME IN CHILDREN

In children under 7 years, Cushing disease is less frequent; adrenal causes of Cushing syndrome (adenoma, carcinoma, or bilateral hyperplasia) are the most common causes of the condition in infants and young toddlers.

In children < 7 y.o:

1. Nodules (carcinoma-70%, adenoma-30%),
2. PBAH- primary bilateral adrenal hyperplasia

- ✓ micronodular: PPNAD -primary pigmented nodular adrenocortical disease, with Carney syndrome, nonpigmented (iMAD- isolated micronodular adrenocortical disease)
- ✓ macronodular (BMH-bilateral macronodular hiperplasia): McCune syndrome, Albright syndrome, MMAD-massive macronodular arenal hyperplasia, AIMAH-adrenocorticotropin independent macronodular adrenocortical hyperplasia

Postać kliniczna ZC	Mutacje genów i zaburzenie ekspresji białek
Choroba Cushinga	MEN1, USP8, CDKis, AIP, CDKN1B, SDHx, DICER1; Brg1, HDAC2, TP4, PTTG, EGFR
Ekotopowa sekrecja ACTH	RET(MEN2), MEN1,
BMAH	ARMC5, MEN1, FH, GNAS1, PDE11A, PDE8B, MC2R, PRKACA, DOTL1, HDAC9, PRUNE2; GPCR, POMC/ACTH, PRKR1A,
Gruczolaki nadnercza	PRKACA, CTNNB1, GNAS1, PRKR1A, ; GPCR, PRKR1A,
PPNAD	PRKR1A, PDE11A, PDE8B, PRKACA, PRKACB; PRKACA
Rak nadnercza	MEN1, GNAS1, H-19, CDK1, IGF-2 ; CHEK2, TP53

ETIOLOGY OF CUSHING SYNDROME

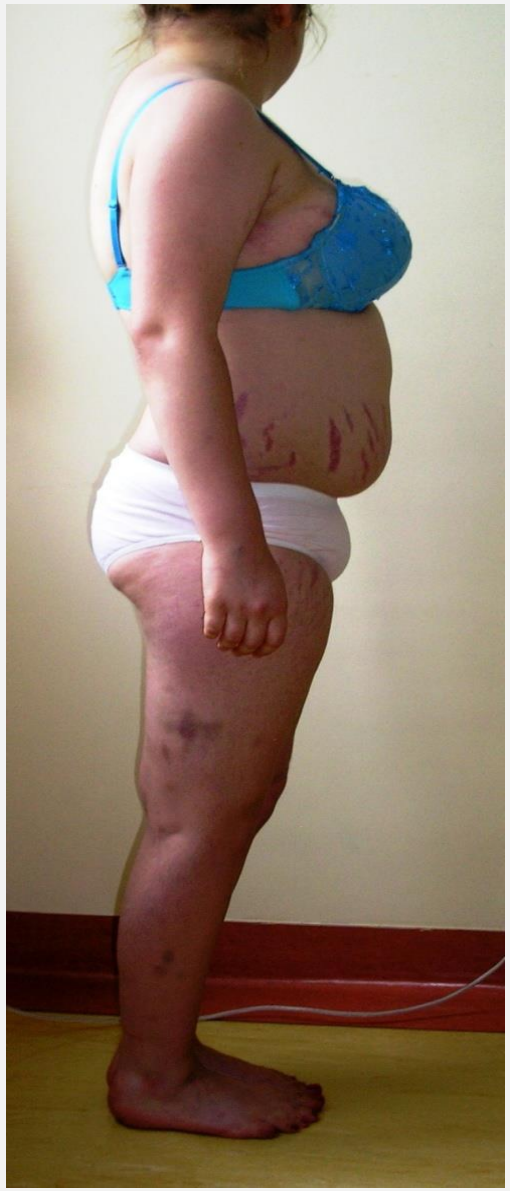
- Autonomous secretion of cortisol from the adrenal glands, or ACTH-independent Cushing syndrome, accounts for approximately 15% of all the cases of Cushing syndrome in childhood.
- In prepubertal children, adrenocortical lesions are the most frequent cause of Cushing syndrome. Adrenocortical neoplasms account for 0.6% of all childhood tumors; Cushing syndrome is a manifestation of approximately one third of all adrenal tumors.

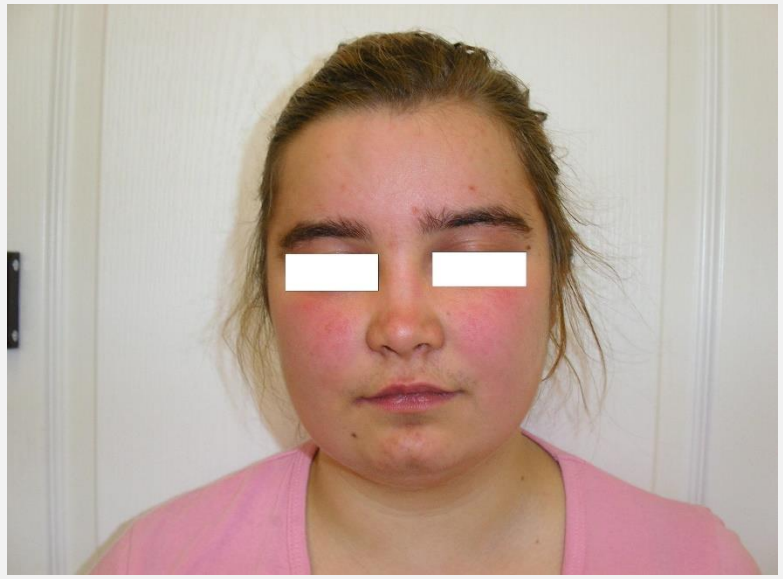
CUSHING SYNDROME ETIOLOGY

- In young children, unilateral (single) adrenal tumors presenting with Cushing syndrome are often malignant (more than 70%). Most patients present under age 5, contributing thus to the first peak of the known bimodal distribution of adrenal cancer across the life span. As in adults, there is a female-to-male predominance.
- The tumors usually occur unilaterally; however, in 2% to 10% of patients they occur bilaterally. Recently, bilateral nodular adrenal disease has been appreciated as a more frequent than previously thought cause of Cushing syndrome in childhood.

PPNAD – PRIMARY PIGMENTED ADRENOCORTICAL NODULAR DISEASE

- Primary pigmented adrenocortical nodular disease (PPNAD) is a genetic disorder associated with germline inactivating mutations of the PRKAR1A gene
- The majority of cases is associated with Carney complex, a syndrome of multiple endocrine gland abnormalities
- The adrenal glands in PPNAD are most commonly normal or even small in size, with multiple pigmented nodules usually (but not always) surrounded by an atrophic cortex. The nodules are autonomously functioning, resulting in the surrounding atrophy of the cortex. Children and adolescents with PPNAD frequently have periodic, cyclical, or otherwise atypical Cushing syndrome





PPNAD

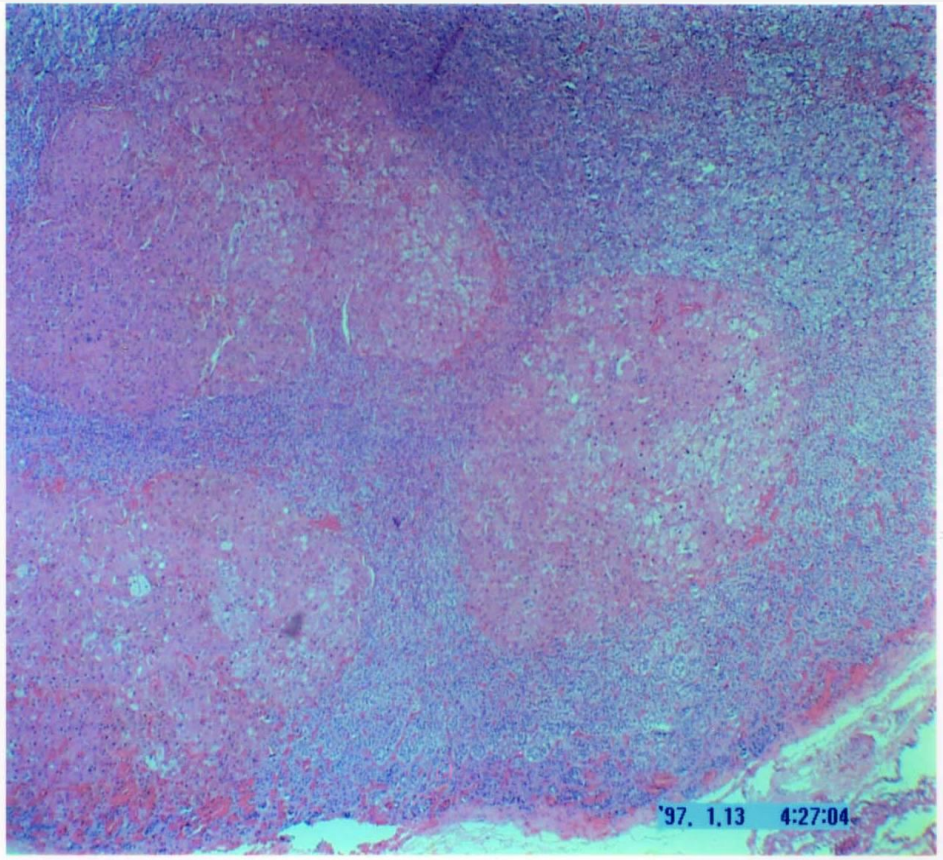
ACTH: 5,3 pg/ml

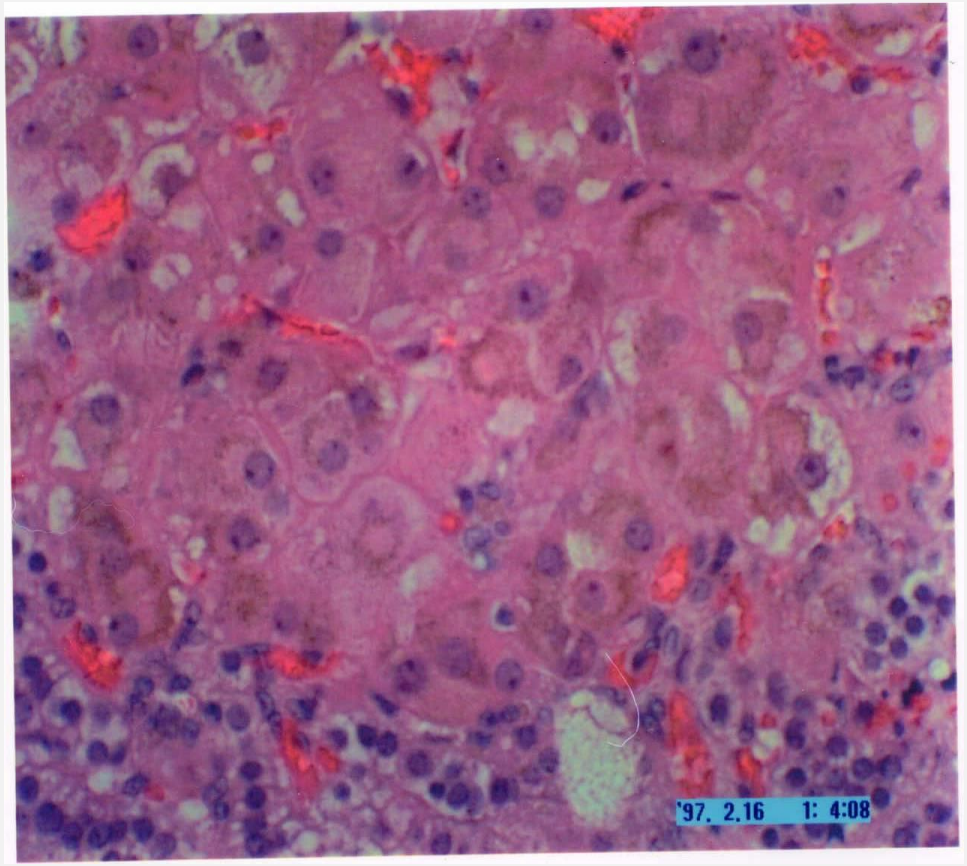
Kortyzol	8:00	20:00
kortyzol [ug/dl] (N =6,2-19,4)	20,3	24,2

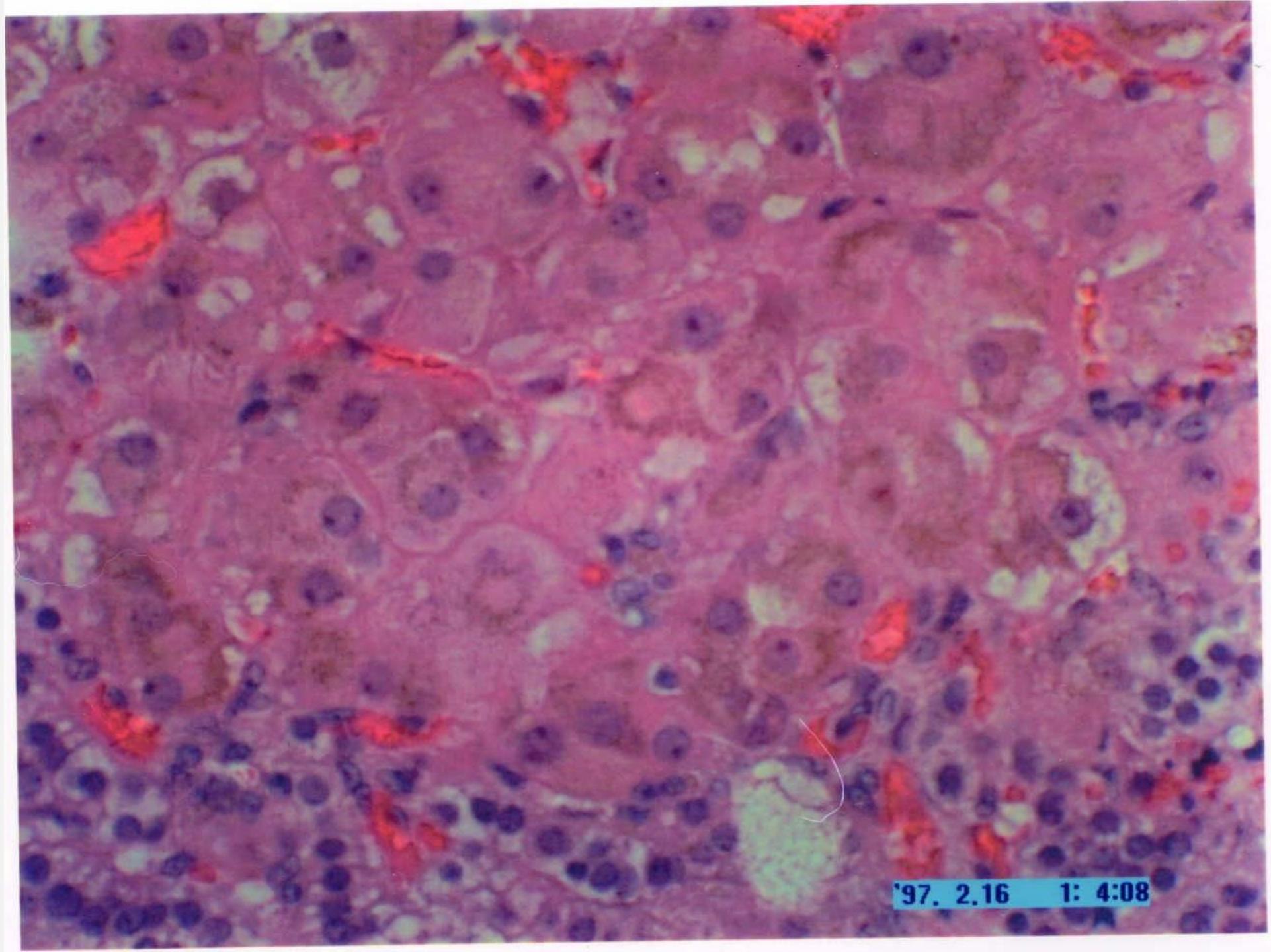
Test z dxm

doba	0	II	IV	VI	VIII
kortyzol -DZM [mmol/24godz]	162	1180	2120	4116	3000

PPNAD HIST-PATH. OF ADRENAL GLAND



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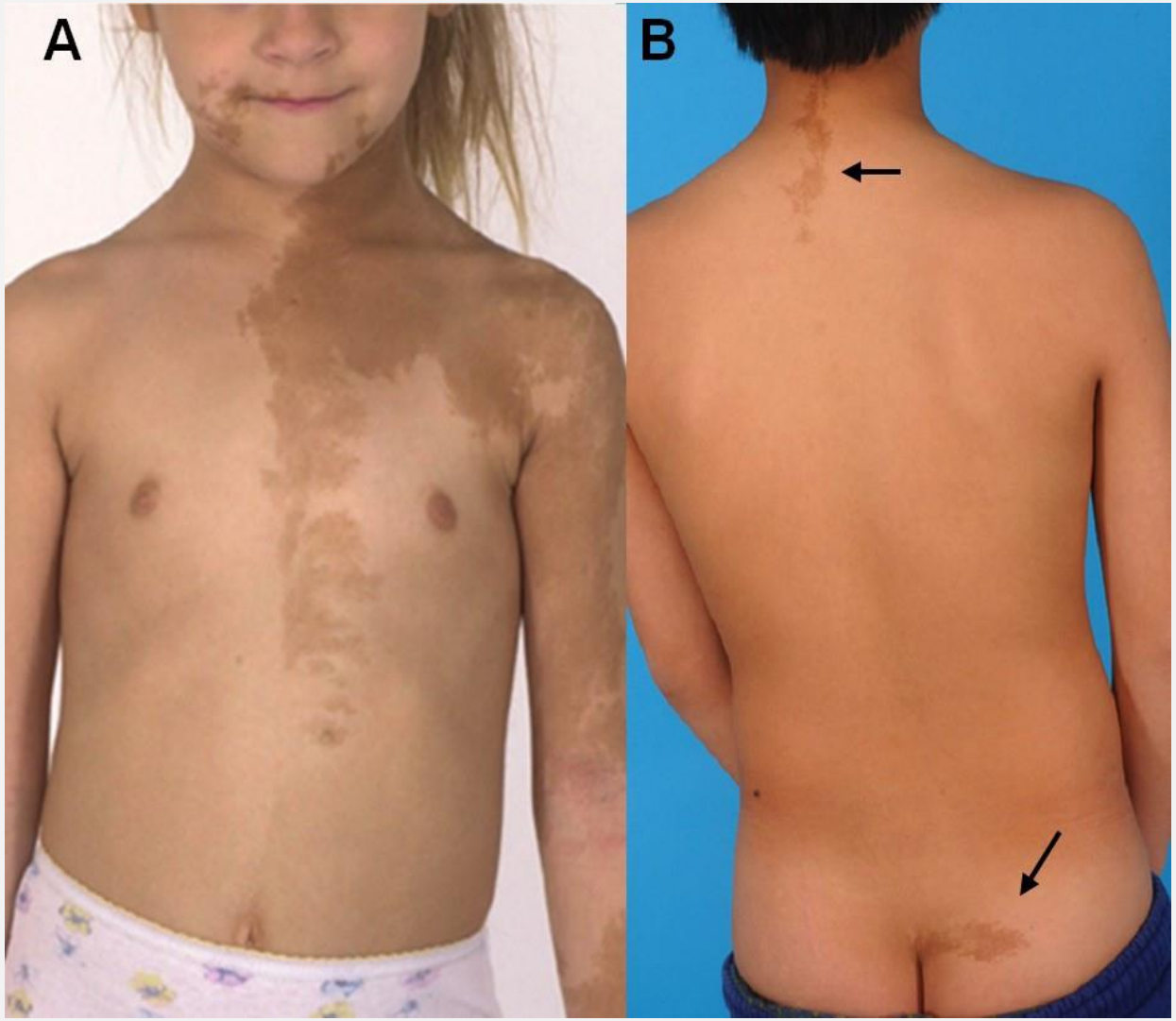
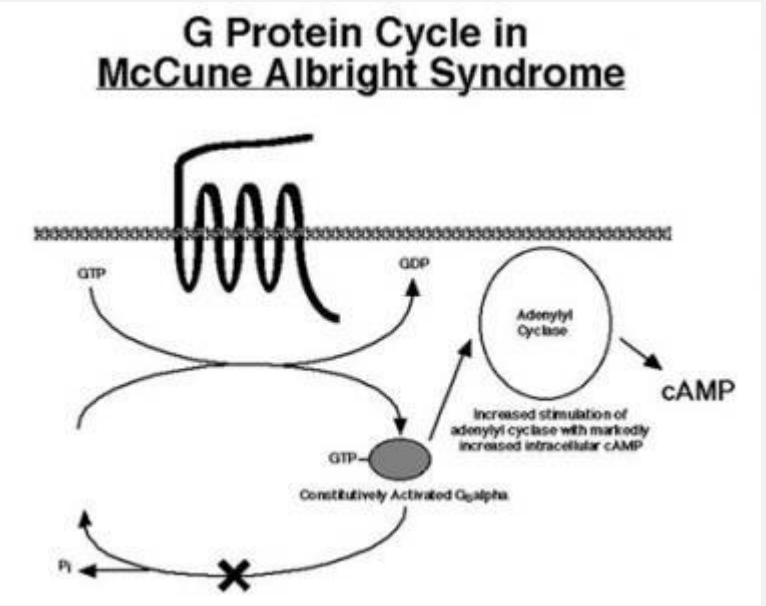
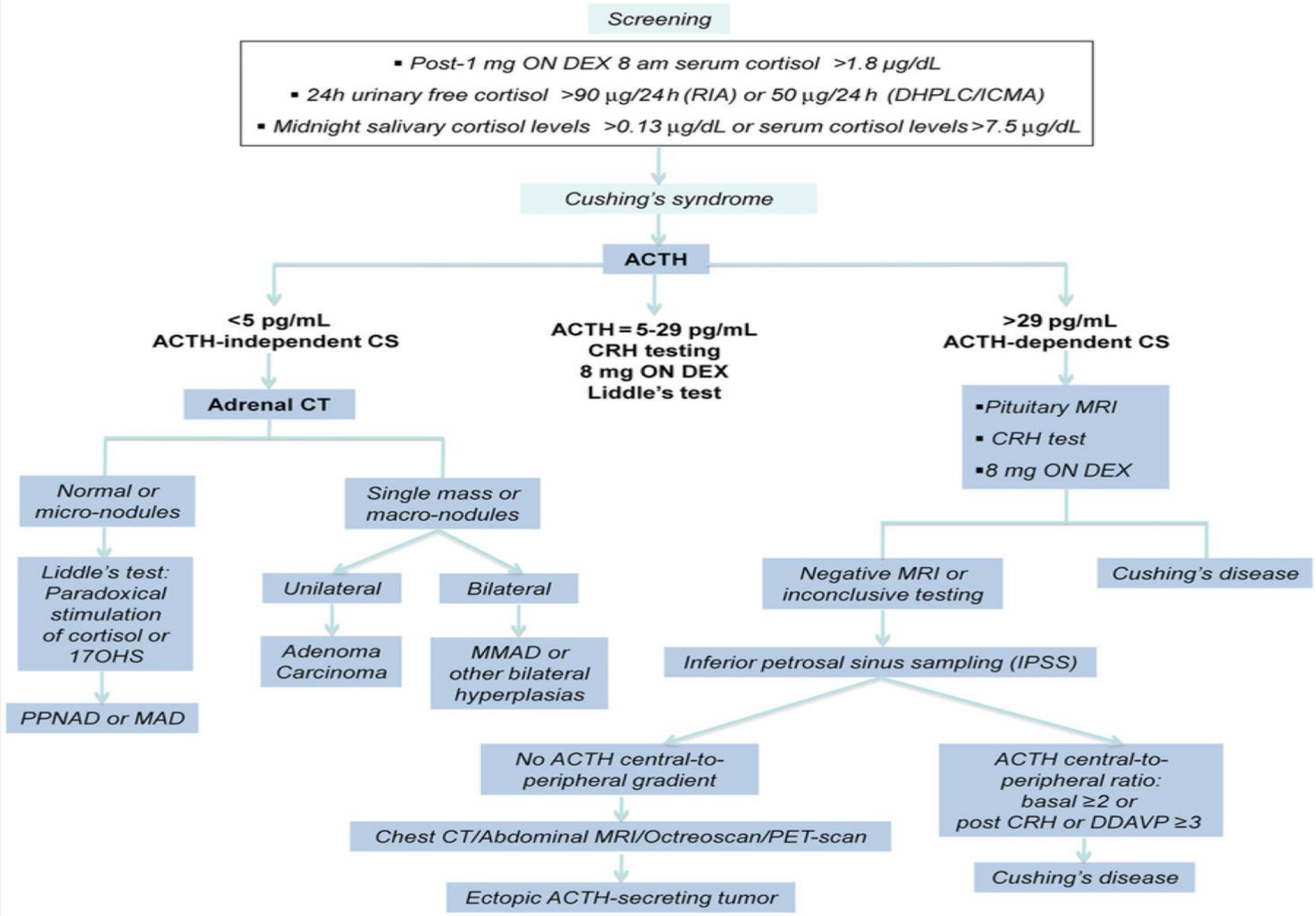
MMAD- MASSIVE MACRONODULAR ADRENAL HYPERPLASIA

- In MMAD , the adrenal glands are massively enlarged, with multiple, huge nodules that are typical yellow-to-brown cortisol-producing adenomas. Most cases of MMAD are sporadic, although a few familial cases have been described; in those cases, the disease appears in children.
- In some patients with MMAD, cortisol levels appear to increase with food ingestion (food-dependent Cushing syndrome). These patients have an aberrant expression of the gastric inhibitory polypeptide receptor (GIPR) in the adrenal glands.
- Adrenal adenomas or, more frequently, bilateral macronodular adrenal hyperplasia can also be seen in McCune Albright syndrome (MAS). In this syndrome, there is a somatic mutation of the GNAS1 gene leading to constitutive activation of the Gsα protein and continuous, non-ACTH-dependent activation of steroidogenesis by the adrenal cortex. Cushing syndrome in MAS is rare and usually presents in the infantile period (before 6 months of age); interestingly, a few children have had spontaneous resolution of their Cushing syndrome. Aberrant cyclic adenosine monophosphate (cAMP) signaling has been linked to almost all genetic forms of adrenal-dependent cortisol excess.



Skin pigmentation in McCune Albright Syndrome




Screening
▪ Post-1 mg ON DEX 8 am serum cortisol >1.8 µg/dL
▪ 24h urinary free cortisol >90 µg/24 h (RIA) or 50 µg/24 h (DHPLC/ICMA)
▪ Midnight salivary cortisol levels >0.13 µg/dL or serum cortisol levels >7.5 µg/dL
Cushing's syndrome
ACTH
<5 pg/mL
ACTH-independent CS
ACTH = 5-29 pg/mL
CRH testing
8 mg ON DEX
Liddle's test
>29 pg/mL
ACTH-dependent CS
Adrenal CT
▪ Pituitary MRI
▪ CRH test
▪ 8 mg ON DEX
Normal or micro-nodules
Single mass or macro-nodules
Liddle's test: Paradoxical stimulation of cortisol or 17OHS
Unilateral
Bilateral
Negative MRI or inconclusive testing
Cushing's disease
PPNAD or MAD
Adenoma Carcinoma
MMAD or other bilateral hyperplasias
Inferior petrosal sinus sampling (IPSS)
No ACTH central-to-peripheral gradient
ACTH central-to-peripheral ratio: basal ≥2 or post CRH or DDAVP ≥3
Chest CT/Abdominal MRI/Octreoscan/PET-scan
Cushing's disease
Ectopic ACTH-secreting tumor

DIAGNOSTIC GUIDELINES

1. The medical history and clinical evaluation, including review of growth data, are important to make the initial diagnosis of Cushing syndrome.

2. Laboratory and imaging confirmations.

An algorithm of the diagnostic proces:

The first step in the diagnosis of Cushing syndrome is to document hypercortisolism.

- One excellent screening test for hypercortisolism is a 24-hour urinary free cortisol (UFC) excretion (corrected for body surface area). Falsely high UFC may be obtained because of physical and emotional stress, chronic and severe obesity, pregnancy, chronic exercise, depression, poor diabetes control, alcoholism, anorexia, narcotic withdrawal, anxiety, malnutrition, and high water intake. These conditions may cause sufficiently high UFCs to cause what is known as pseudo-Cushing syndrome.

DIAGNOSTIC GUIDELINES

- Another baseline test for the establishment of the diagnosis of Cushing syndrome is a low dose dexamethasone suppression test. This test involves giving 1 mg of dexamethasone at 11 PM.measuring a serum cortisol level the following morning at 8 AM. If the serum cortisol level is greater than 1.8 μg/dL, further evaluation is necessary.

TREATMENT

Medical:

Ketokonazol Metyrapon, Aminoglutetymid, Mitotan

Surgical (selective transsphenoidal resection of ACTH-secreting pituitary adenomas)

Radiotherapy

TREATMENT

- The treatment of choice for almost all patients with an ACTH-secreting pituitary adenoma (Cushing disease) is transsphenoidal surgery (TSS).
- Postoperative complications include transient diabetes insipidus (DI) and, occasionally, syndrome of inappropriate antidiuretic hormone secretion (SIADH), central hypothyroidism, growth hormone deficiency, hypogonadism, bleeding, infection (meningitis), and pituitary apoplexy. The mortality rate is extremely low, at less than 1%. Permanent pituitary dysfunction (partial or pan-hypopituitarism) and DI are rare but they are more likely after repeat TSS or larger adenomas.
- Pituitary irradiation is considered an appropriate treatment in patients with Cushing disease following a failed TSS. Up to 80% of patients will have remission after irradiation of the pituitary gland. Hypopituitarism is the most common adverse effect, and it is more frequent when surgery precedes the radiotherapy. The recommended dosage is 4500/5000 cGy total, usually given over a period of 6 weeks. Newer forms of stereotactic radiotherapy are now available as options for treatment of ACTH-secreting pituitary tumors. Photon knife (computer-assisted linear accelerator) or thegamma knife (cobalt –60) approaches are now available; however, experience with these techniques is limited, especially in children. These modalities may be attractive because of the smaller amount of time required for these procedures and the possibility for fewer adverse effects.

TREATMENT

- The treatment of choice for benign adrenal tumors is surgical resection, laparoscopic adrenalectomy.
- Adrenal carcinomas may also be surgically resected, unless at later stages. Solitary metastases should be removed, if possible.
- Therapy with mitotane, which is an adrenocytolytic agent, can be used as an adjuvant therapy or in the case of an inoperable tumor. Other chemotherapeutic options include cisplatin, 5-flourouracil, suramin, doxorubicin, and etoposide.
- Occasionally glucocorticoid antagonists and steroid synthesis inhibitors are needed to correct the hypercortisolism. Radiotherapy can also be used in the case of metastases. The prognosis for adrenal carcinoma is poor, but usually children have a better prognosis than adults.

TREATMENT

- Bilateral total adrenalectomy is usually the treatment of choice in bilateral micronodular or macronodular adrenal disease, such as PPNAD and MMAD. In addition, adrenalectomy may be considered as a treatment for those patients with Cushing disease or ectopic ACTHdependent
- Cushing syndrome who have either failed surgery or radiotherapy, or their tumor has not been localized, respectively. Nelson syndrome, which includes increased pigmentation, elevated ACTH levels, and a growing pituitary ACTH-producing pituitary tumor, may develop in up to 15% of patients with Cushing disease who are treated with bilateral adrenalectomy. It is possible that children with untreated Cushing disease are especially vulnerable to Nelson syndrome after bilateral adrenalectomy.

TREATMENT

- Glucocorticoids should be replaced at the physiologic replacement dose (12–15 mg/m2/day 2 or 3 Times daily).
- In the immediate postoperative period, stress doses of cortisol should be initiated.
- After bilateral adrenalectomy, patients require lifetime replacement with both glucocorticoids (as described previously) and mineralocorticoids (fludrocortisone 0.1–0.3 mg daily). These patients also need stress doses of glucocorticoids immediately postoperatively; they are weaned to physiologic replacement relatively quickly. In addition, stress dosing for acute illness, trauma, or surgical procedures is required for both temporary and permanent adrenal insufficiency.

PSYCHOSOCIAL IMPLICATIONS

- Cushing syndrome has been associated with multiple psychiatric and psychological disturbances, most commonly emotional lability, depression, and/or anxiety.
- Other abnormalities have included mania, panic disorder, suicidal ideation, schizophrenia, obsessive–compulsive symptomatology, psychosis, impaired self-esteem, and distorted body image.
- Significant psychopathology can even remain after remission of hypercortisolism and even after recovery of the HPA axis.