Endocrinology „take home” messages

1

Agenda:

1. Diabetes: diagnosis, DKA and hypoglycemia
2. Adrenals: Addisonian crisis, CAH
3. Thyroid gland: Hypothyroidism, hyperthyroidism
4. Puberty timetable & tricks
5. Growth

2

Agenda:

1. Diabetes: diagnosis, DKA and hypoglycemia
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4. Puberty: metabolic & trivia
5. Growth

3

Criteria for the Diagnosis of Diabetes

A1C ≥6.5%

OR

Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

OR

2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT

OR

A random plasma glucose ≥200 mg/dL (11.1 mmol/L)

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 2.

4

Criteria for the Diagnosis of Diabetes

A1C ≥6.5%

The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay*

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 2.

5

Criteria for the Diagnosis of Diabetes

Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

Fasting is defined as no caloric intake for at least 8 h*

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 2.

6

Criteria for the Diagnosis of Diabetes

2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT

The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water*

*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 2.

7

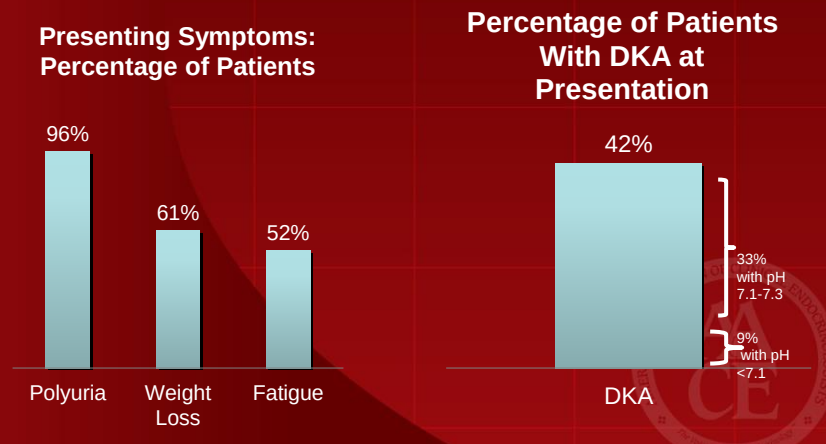
Criteria for the Diagnosis of Diabetes

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L)

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 2.

8

Symptoms and Severity of T1DM at Presentation: EURODIAB



9

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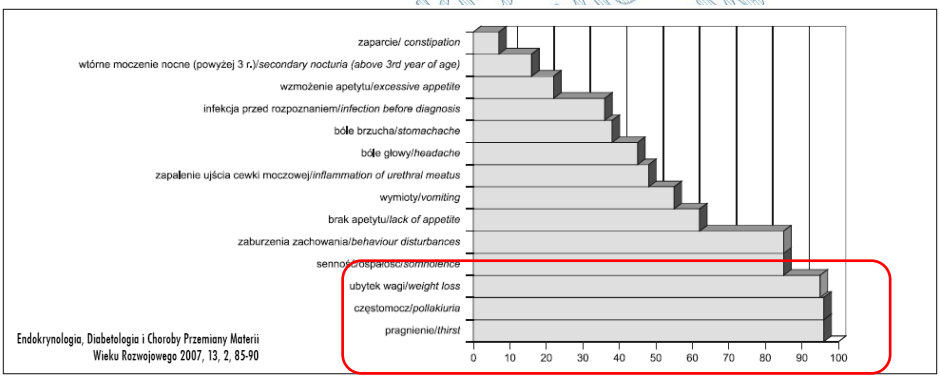
DKA, diabetic ketoacidosis.
Levy-Marchal C, et al. *Diabetol*. 2001;44 (Suppl 3):B75-B80.

9

Ocena występowania i analiza wybranych czynników ryzyka kwasicy ketonowej w momencie ujawnienia cukrzycy typu 1

The occurrence and analysis of chosen risk factors of DKA among children with new onset of DMT1

Bogusława Olak-Białoń, Grażyna Deja, Przemysława Jarosz-Chobot, Ewa Otto Buczkowska



Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego 2007, 13, 2, 85-90

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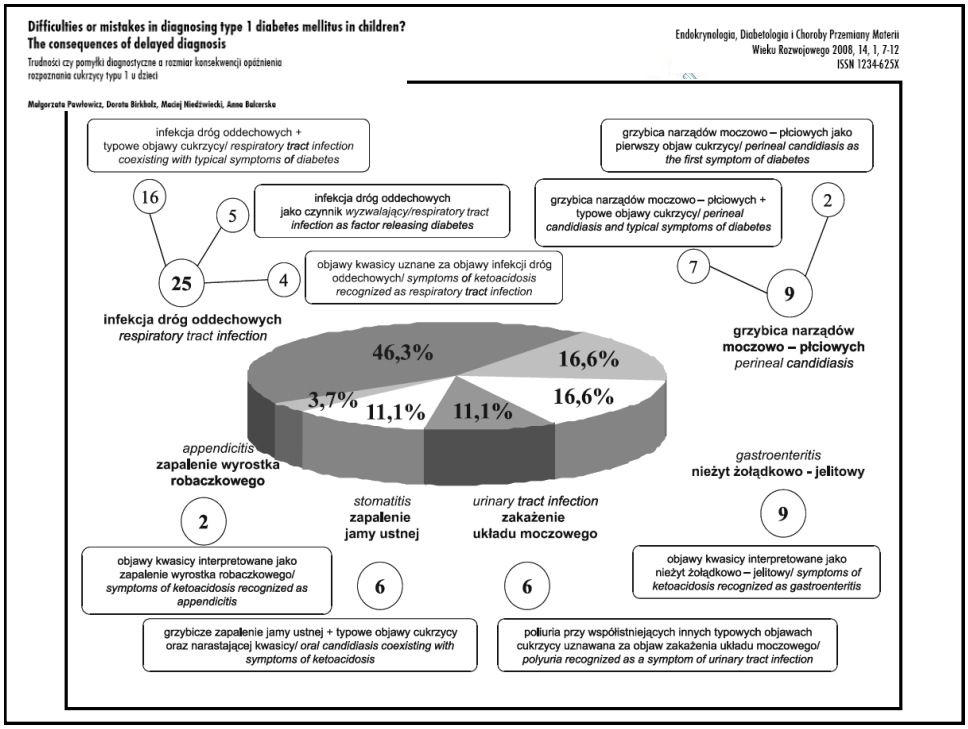

11

Prediabetes: IFG, IGT, Increased A1C

Categories of increased risk for diabetes (prediabetes)*

FPG 100–125 mg/dL (5.6–6.9 mmol/L): IFG

OR

2-h plasma glucose in the 75-g OGTT 140–199 mg/dL (7.8–11.0 mmol/L): IGT

OR

A1C 5.7–6.4%

*For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S13; Table 3.

12

Classification of Diabetes

- Type 1 diabetes
  - β-cell destruction
- Type 2 diabetes
  - Progressive insulin secretory defect
- Other specific types of diabetes
  - Genetic defects in β-cell function, insulin action
  - Diseases of the exocrine pancreas
  - Drug- or chemical-induced
- Gestational diabetes mellitus (GDM)

ADA. I. Classification and Diagnosis. *Diabetes Care* 2013;36(suppl 1):S11.

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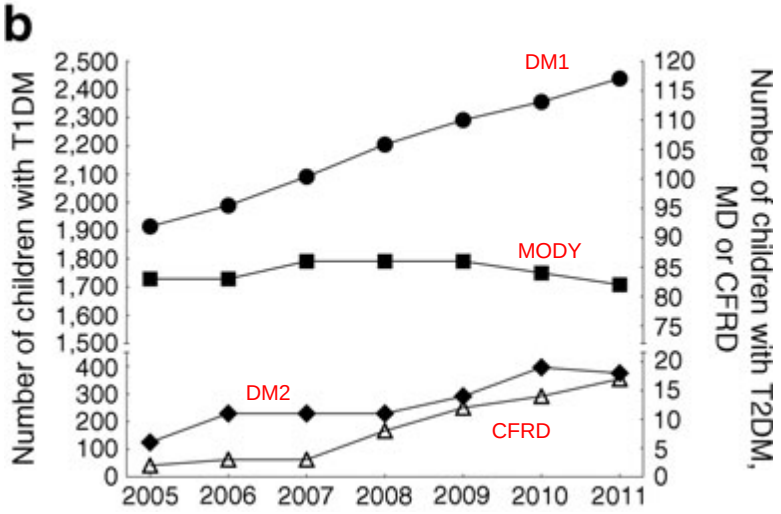
DM EPIDEMIOLOGY IN POLAND

W. Fendler i wsp. Diabetologia (2012) 55:2631–2635



14

Classifying Diabetes

<table>
<tr><td rowspan="2">High-risk HLA*:
(10% of population)
DR3/4,DQ1B1*0302
DR4/4, DR4/8
DR4/1, DR4/9
DR3/3</td><td rowspan="2">IAA+
GADA+
IA-2A+ or
ZnT8A+</td><td colspan="2">Autoantibody negative at onset</td></tr>
<tr><td colspan="2">C-peptide (ng/mL)</td></tr>
<tr><td>HLA+</td><td colspan="3" rowspan="2">T1aD = 80%</td></tr>
<tr><td>HLA-</td><td>T1b
5%</td><td>T2D
10%</td></tr>
</table>

IAA, autoantibodies to insulin; GADA, glutamic acid decarboxylase; IA-2A, the tyrosine phosphatase insulinoma antigen; ZnT8A, zinc transporter 8; T1aD, type 1a (autoimmune) diabetes; T2D, type 2 diabetes.
*Needs to be refined for non-white population groups.
Rewers M. *Diabetes Metab J.* 2012;36:90-97.

15
AACE Diabetes Resource Center

15

A Growing Issue: Differentiating T1DM and T2DM

	Type 1 Diabetes	Type 2 Diabetes
Usual clinical course	Insulin-dependent	Initially non-insulin-dependent
Usual age of onset	<20 years (but ~50% over 20 years)	>40 years but increasingly earlier
Body weight	Usually lean	Usually obese
Onset	Often acute	Subtle, slow
Ketosis prone	Yes	No
Family history	≤15% with 1st-degree relative	Common
Ethnicity	Predominantly white	More common in minorities
Frequency of HLA-DR3, DR4, DQB1*0201, *0302	Increased	Not increased
Islet autoantibodies (GADA, ICA, IA-2A, IAA)	Present	Absent

IAA, autoantibodies to insulin; GADA, glutamic acid decarboxylase; IA-2A, the tyrosine phosphatase insulinoma antigen; ZnT8A, zinc transporter 8; T1aD, type 1a (autoimmune) diabetes; T2D, type 2 diabetes.
*Needs to be refined for nonwhite population groups.
Rewers M. *Diabetes Metab J.* 2012;36:90-97.

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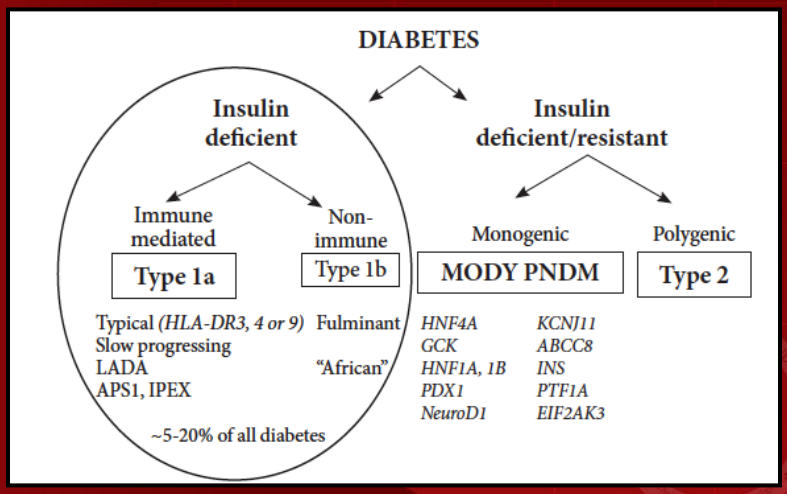
16

"Etiological" Classification of Diabetes



17

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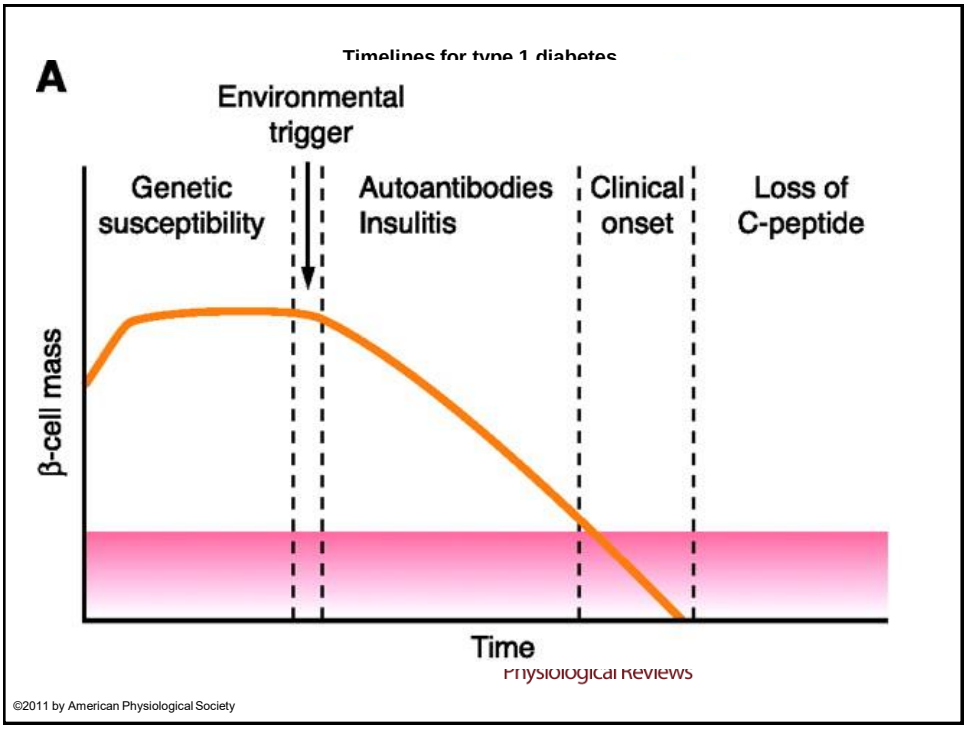
APS1, autoimmune polyendocrine syndromes 1; IPEX, immunodeficiency, polyendocrinopathy, enteropathy, X-linked syndrome; MODY, maturity-onset diabetes of the young.
Rewers M. *Diabetes Metab J.* 2012;36:90-97.

17

Type 1 diabetes

- Type 1 diabetes is a chronic autoimmune disease associated with selective islet β-cell destruction that leads to insulin-dependency.

18



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Diabetes complications:

- Acute:
- Ketoacidosis
- Hypoglycemia
- Chronic:
- Nephropathy
- Retinopathy
- Neuropathy (symmeric, autonomic)

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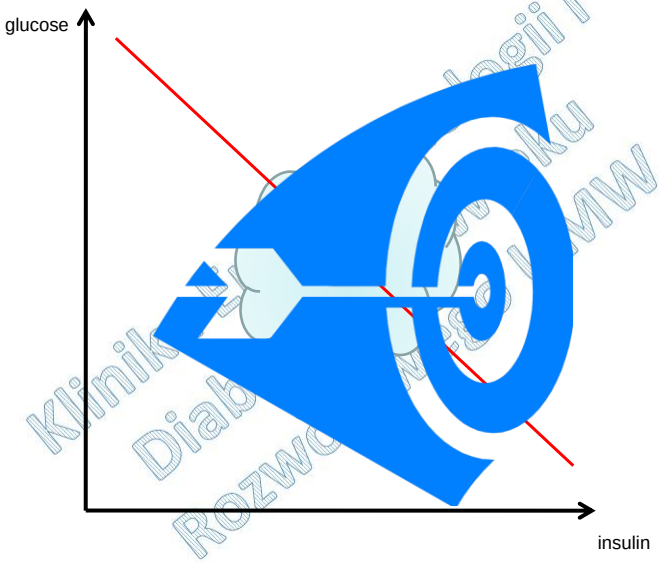

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„It is easier to judge, if you don't know all circumstances"

Lower BG

- Insulin
- Exercise

Higher BG

- Food
- Stress
- Illness

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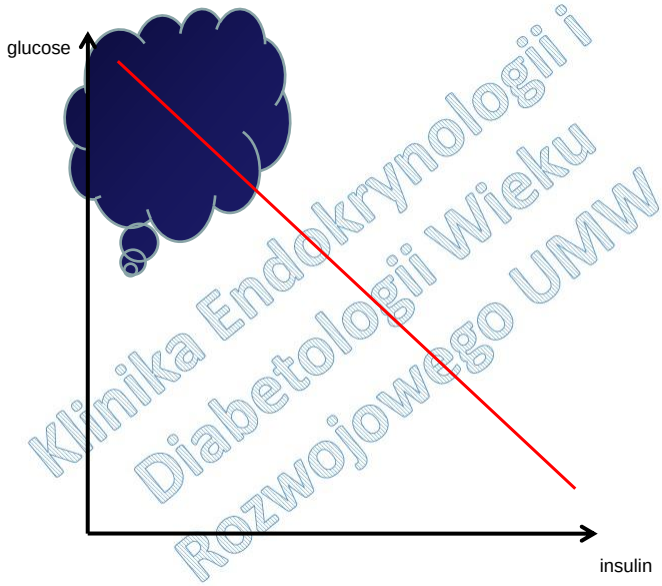

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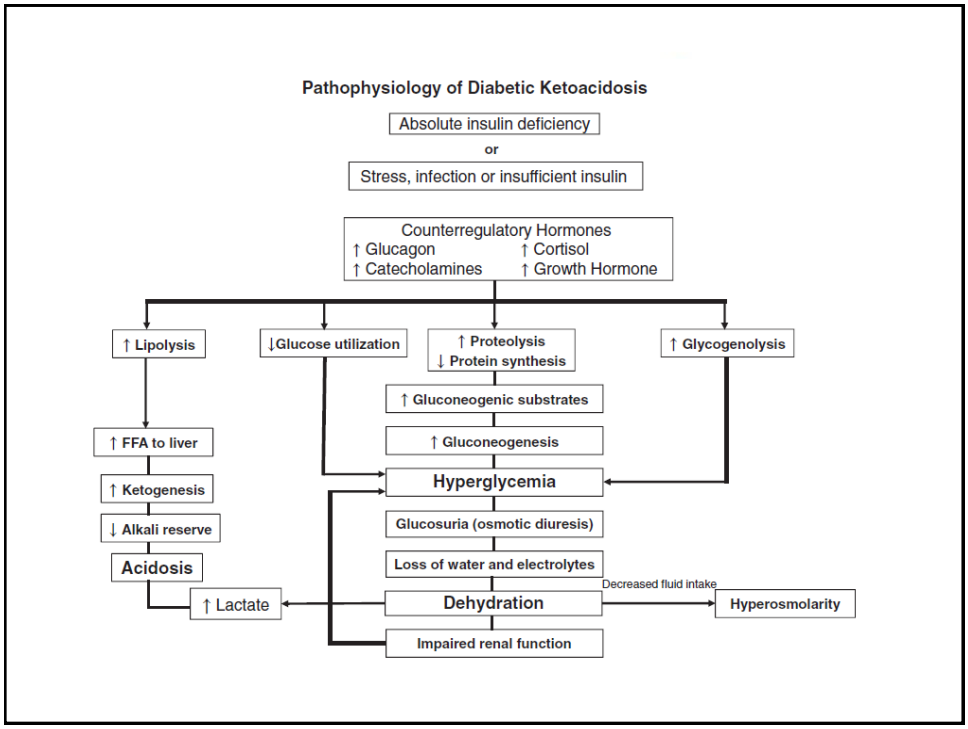
Ketoacidosis:

- Acute insulin deficiency leads to diabetic ketoacidosis
- Causes:
  - Infections (especially with diarrhea and vomiting)
  - Diet non-compliance
  - Inappropriate insulin supply (not adequate dose, omitting the dose, injection device's failure)

24



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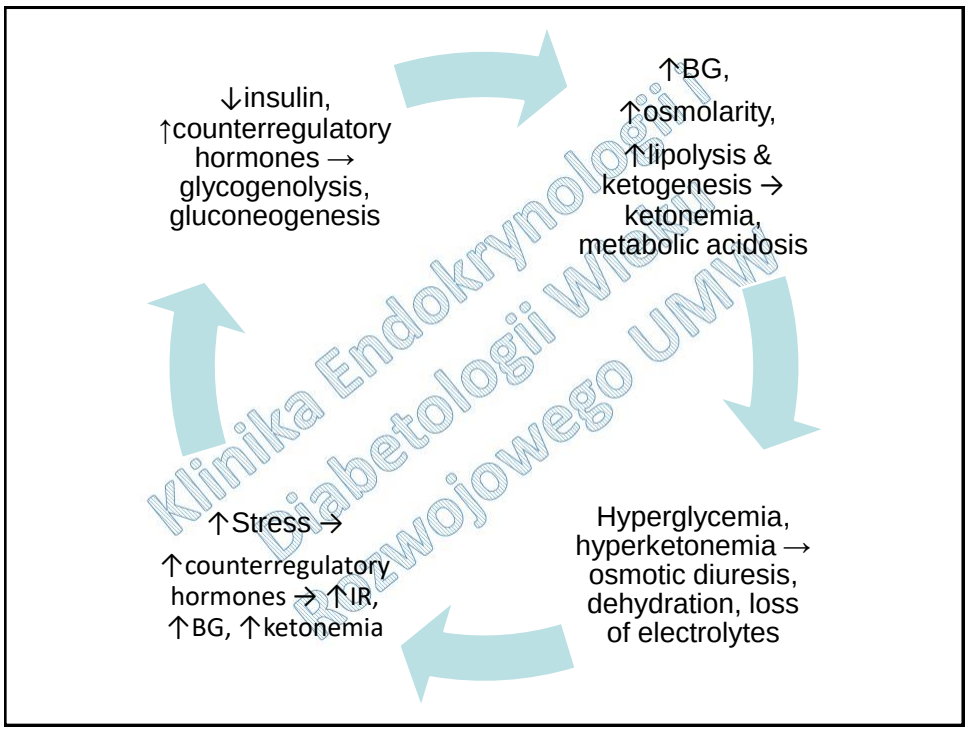

26

- If this vicious circle will not be interrupted with insulin and electrolytes administration and rehydration of the patient, the DKA and dehydration will lead to one's death.

27

Definition of diabetic ketoacidosis (DKA)

The **biochemical criteria** for the diagnosis of DKA are (5):

- Hyperglycemia (blood glucose >11 mmol/L [≈200 mg/dL])
- Venous pH <7.3 or bicarbonate <15 mmol/L
- Ketonemia and ketonuria.

The **severity of DKA** is categorized by the degree of acidosis (18):

- Mild: venous pH <7.3 or bicarbonate <15 mmol/L
- Moderate: pH <7.2, bicarbonate <10 mmol/L
- Severe: pH <7.1, bicarbonate <5 mmol/L

Pediatric Diabetes 2009: **10** (Suppl. 12): 118–133

28

Clinical manifestations of diabetic ketoacidosis

- Dehydration
- Tachypnea; deep, sighing (Kussmaul) respiration
- Nausea, vomiting, and abdominal pain that may mimic an acute abdominal condition
- Confusion, drowsiness, progressive obtundation, and loss of consciousness

29

Goals of therapy

- Correct dehydration
- Correct acidosis and reverse ketosis
- Restore blood glucose to near normal
- Avoid complications of therapy
- Identify and treat any precipitating event

Pediatric Diabetes 2009: **10** (Suppl. 12): 118–133

30

Table 1. Losses of fluids and electrolytes in diabetic ketoacidosis and maintenance requirements in normal children

	Average (range) losses per kg	24-hour maintenance requirements	
Water	70 mL (30–100)	*≤10 kg	100 mL/kg/24 hr
		11–20 kg	1000 mL + 50 mL/kg/24 hr for each kg from 11–20
		>20 kg	1500 mL + 20 mL/kg/24 hr for each kg >20
Sodium	6 mmol (5–13)		2–4 mmol†
Potassium	5 mmol (3–6)		2–3 mmol
vChloride	4 mmol (3–9)		2–3 mmol
Phosphate	(0.5–2.5) mmol		1–2 mmol

Data are from measurements in only a few children and adolescents (45–49). In any individual patient, actual losses may be less or greater than the ranges shown in Table 1 (E). Three methods for determining maintenance water requirements in children are commonly used: *the Holliday-Segar formula (50) (shown in Table 1), a simplified Holliday-Segar formula (see below and Appendix), and a formula based on body surface area for children more than 10 kg (1,500 mL/m^2/24 hr) (51).
† Maintenance electrolyte requirements in children are per 100 mL of maintenance IV fluid (51, 52).
† Simplified method based on Holliday-Segar: <10 kg 4 mL/kg/hr; 11–20 kg 40 + 2 mL/kg/hr for each kg between 11 and 20; >20 kg 60 + 1 mL/kg/h for each kg >20.

Pediatric Diabetes 2009: **10** (Suppl. 12): 118–133

31

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DOI: 10.1111/pedi.12701

WILEY

ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state

Joseph I. Wolfsdorf[1] | Nicole Glaser[2] | Michael Agus[1,3] | Maria Fritsch[4] | Ragnar Hanas[5] | Arleta Rewers[6] | Mark A. Sperling[7] | Ethel Codner[8]

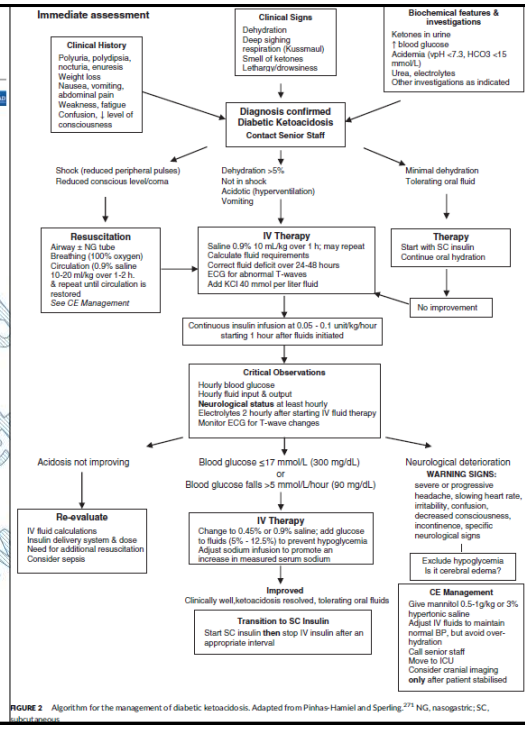
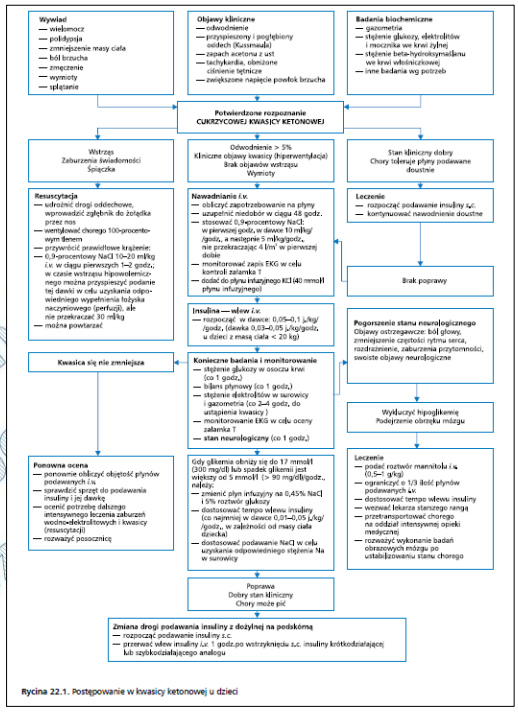


FIGURE 2 Algorithm for the management of diabetic ketoacidosis. Adapted from Pinhas-Hamiel and Sperling.[271] NG, nasogastric; SC, subcutaneous

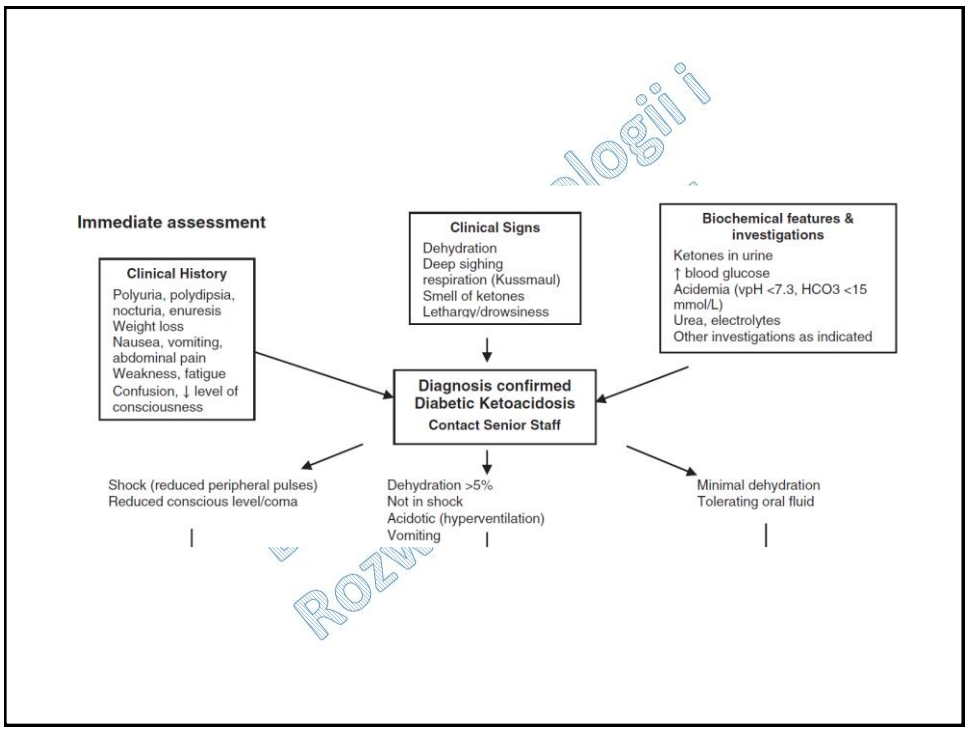
32

Algoritm of DKA therapy
Polish Diabetes
www.cukrzyca.info.pl



Rycina 22.1. Postępowanie w kwasicy ketonowej u dzieci

33



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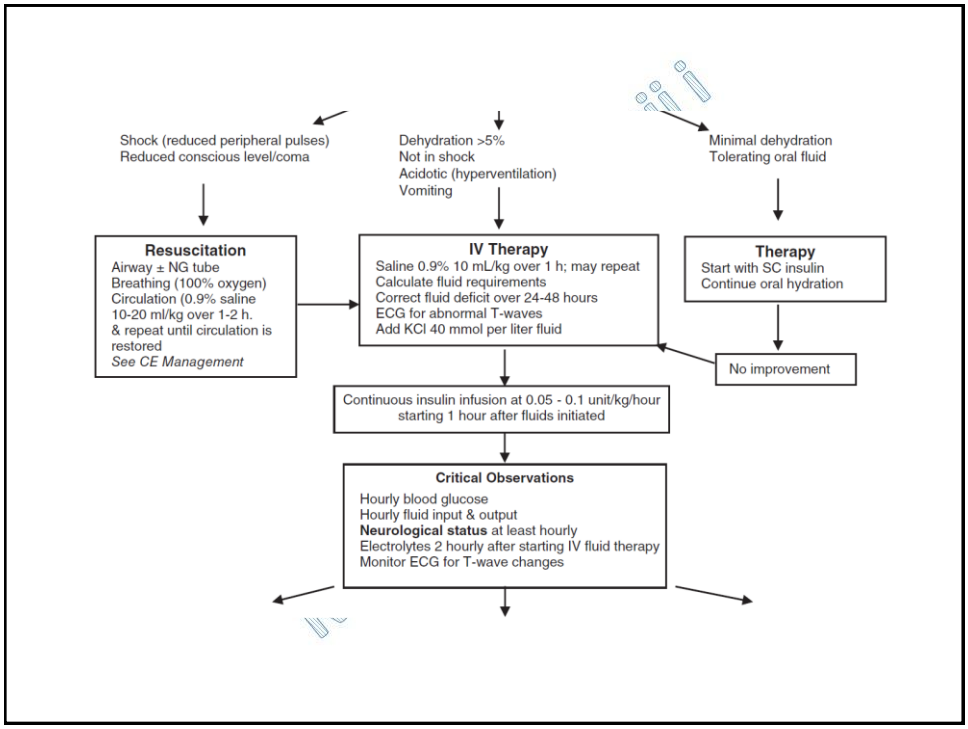
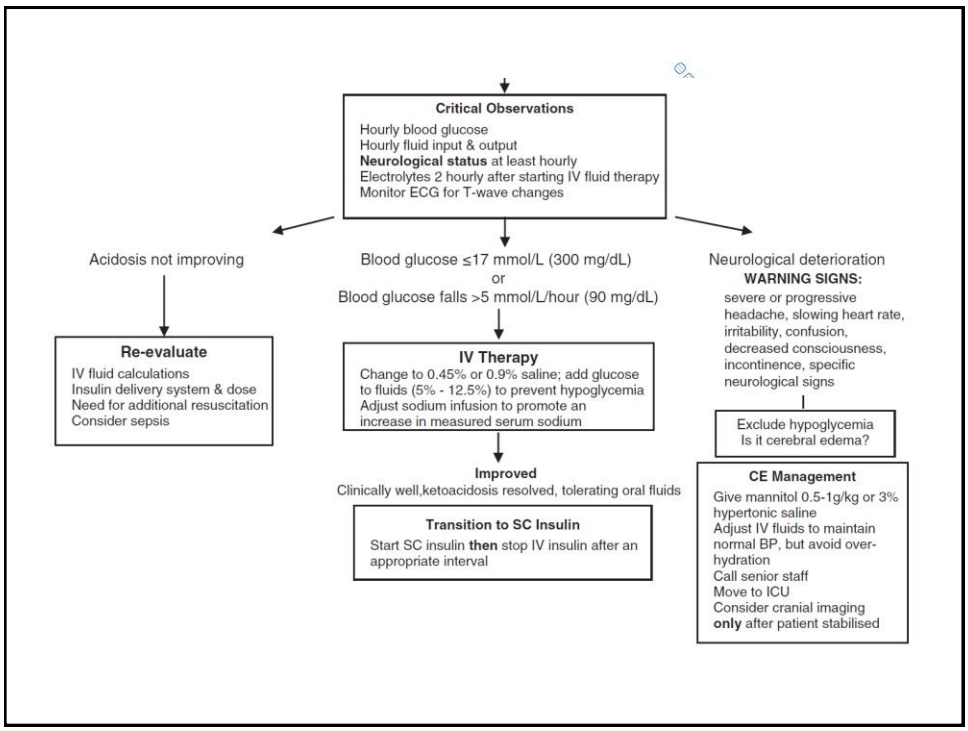

Shock (reduced peripheral pulses)
Reduced conscious level/coma
Dehydration >5%
Not in shock
Acidotic (hyperventilation)
Vomiting
Minimal dehydration
Tolerating oral fluid
Resuscitation
Airway ± NG tube
Breathing (100% oxygen)
Circulation (0.9% saline
10-20 ml/kg over 1-2 h.
& repeat until circulation is restored
See CE Management
IV Therapy
Saline 0.9% 10 mL/kg over 1 h; may repeat
Calculate fluid requirements
Correct fluid deficit over 24-48 hours
ECG for abnormal T-waves
Add KCl 40 mmol per liter fluid
Therapy
Start with SC insulin
Continue oral hydration
No improvement
Continuous insulin infusion at 0.05 - 0.1 unit/kg/hour starting 1 hour after fluids initiated
Critical Observations
Hourly blood glucose
Hourly fluid input & output
Neurological status at least hourly
Electrolytes 2 hourly after starting IV fluid therapy
Monitor ECG for T-wave changes

35


Critical Observations
Hourly blood glucose
Hourly fluid input & output
Neurological status at least hourly
Electrolytes 2 hourly after starting IV fluid therapy
Monitor ECG for T-wave changes
Acidosis not improving
Re-evaluate
IV fluid calculations
Insulin delivery system & dose
Need for additional resuscitation
Consider sepsis
Blood glucose ≤17 mmol/L (300 mg/dL)
or
Blood glucose falls >5 mmol/L/hour (90 mg/dL)
IV Therapy
Change to 0.45% or 0.9% saline; add glucose to fluids (5% - 12.5%) to prevent hypoglycemia
Adjust sodium infusion to promote an increase in measured serum sodium
Improved
Clinically well,ketoacidosis resolved, tolerating oral fluids
Transition to SC Insulin
Start SC insulin then stop IV insulin after an appropriate interval
Neurological deterioration
WARNING SIGNS:
severe or progressive headache, slowing heart rate, irritability, confusion, decreased consciousness, incontinence, specific neurological signs
Exclude hypoglycemia
Is it cerebral edema?
CE Management
Give mannitol 0.5-1g/kg or 3% hypertonic saline
Adjust IV fluids to maintain normal BP, but avoid over-hydration
Call senior staff
Move to ICU
Consider cranial imaging only after patient stabilised

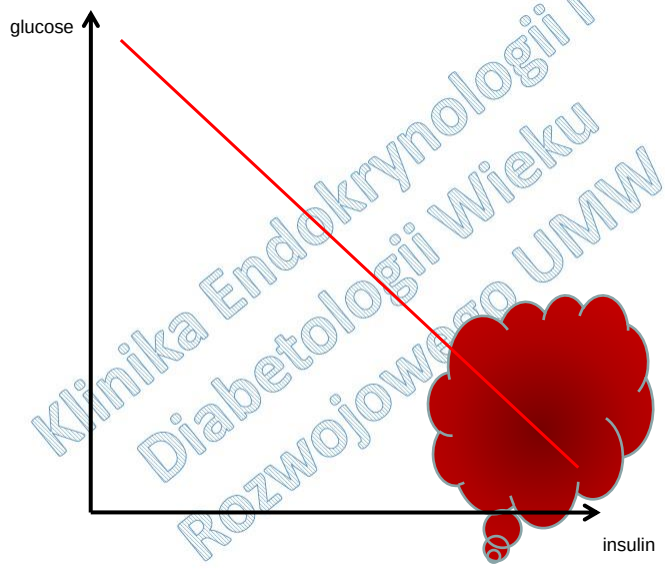
36

AVOID bicarbonate

Severe acidosis is reversible by fluid and insulin replacement; insulin stops further ketoacid production and allows ketoacids to be metabolized, which generates bicarbonate. Treatment of hypovolemia improves tissue perfusion and renal function, thereby increasing the excretion of organic acids.

Controlled trials have shown no clinical benefit from bicarbonate administration.[183–186] Bicarbonate therapy may cause paradoxical CNS acidosis[187,188] and rapid correction of acidosis with bicarbonate causes hypokalemia.[187,189,190] Bicarbonate administration may be beneficial in the rare patient with life-threatening hyperkalemia or unusually severe acidosis (vpH <6.9) that has compromised cardiac contractility.[191]

37



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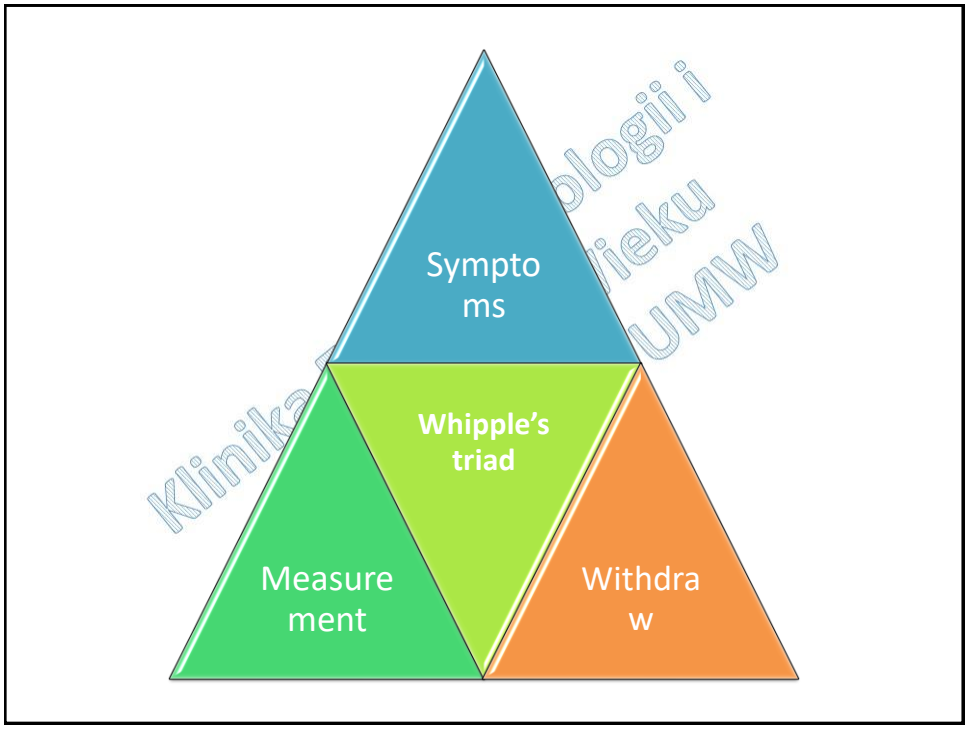


39

Hypoglycemia:

- **Asymptomatic**: blood glucose <55 mg/dl (3mmol/l)
- **Intermediate**: presence of autonomic symptoms
- **Unaware**: **neuroglycopenia**: unusual behavior
- **Severe**: with hypoglycemic coma and central nervous system injury

40

Hypoglycemia symptoms:

CNS (neurological)
- Fatigue
- Dysmnesia
- Concentration difficulties
- Hot flush
- Balance disturbances
- Headache
- Blurred vision, double vision, color blindness
- Loss of consciousness
- Seizures
- Unusual behavior

Autonomic (1)
- Convulsion
- Anxiety
- Palpitation
- Pulsation in thorax
- Numbness of mouth, fingers, tongue
- Excitation
- Starvation
- Nausea
- Pallor
- Sweat

41

Hypoglycemia symptoms

- Occurrence of these symptoms depends on: central nervous system reaction on glucose deficiency and its damage (polyneuropathy), rate of glucose level reduction, age and level of counterregulatory response.
- Children are more sensitive for hypoglycemia - counterregulatory hormones secretion start at glycemia 68 mg/dl (3,8 mmol/l), whereas in adults at 56 mg/dl (3,1mmol/l).

42

Counterregulatory response hormones:

- **Glucagon** (increase glycemia by releasing glucose from hepatic glycogen)
- **Catecholamines** (glycogen, adipose tissue and proteins breakdown)
- **Cortisol** (inhibiting glucose uptake, stimulating adipose tissue and proteins breakdown)
- **Growth hormone** (inhibiting glucose utilization and stimulating adipose tissue metabolism)

43

Hypoglycemia

1. Early (warning) symptoms: trembling, sweat, starvation, tingling sensation, headache.
2. Light neuroglycopenia: double vision, indistinct speech, concentration difficulties
3. Severe neuroglycopenia: violent/unusual behavior, disorientation
4. Loss of consciousness: hemiparesis, seizures

44

Treatment of hypoglycemia

- Light and intermediate, if the patient is conscious: glucose, juice, jelly, a sandwich afterwards
- Severe: the patient is unconscious: **glucagon 0,01mg/kg** body mass. Action profile – onset 10 -15', duration 30-60'
- When the patient become conscious: glucose, juice, jelly, a sandwich.
- Adverse effect of glucagon – nausea, vomiting
- No effect of glucagone if: glycogen reserve is low (exercises, frequent hypoglycemias, starvation), alcohol intake, over dosage of insulin.

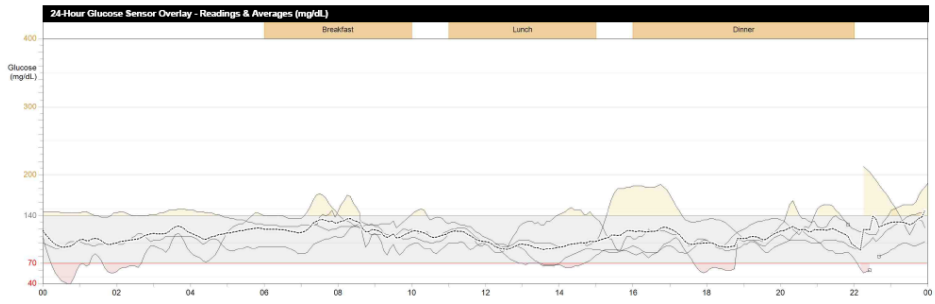
45

Goals of insulin therapy in children:

- Appropriate growth and psychomotor development
- Appropriate social development
- Appropriate personal development
- To lower the risk of complications

46

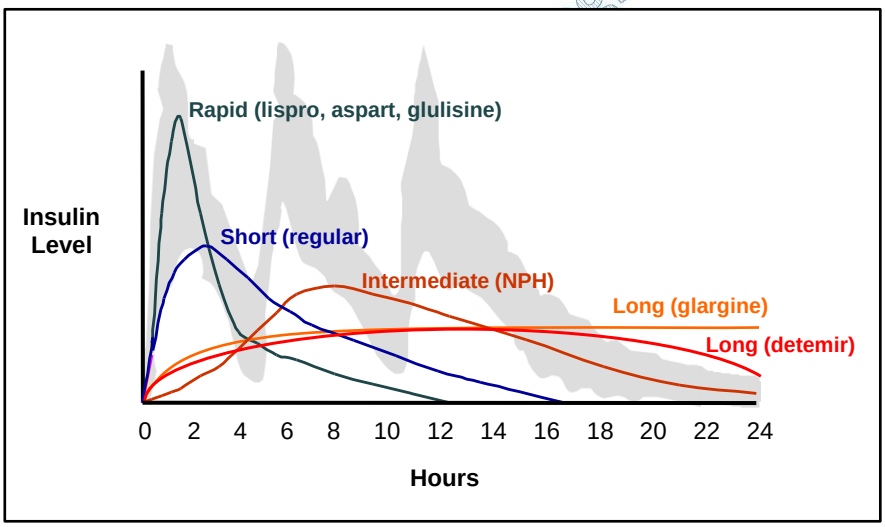
Goals



– Near-normoglycemia
– As few hypos as possible

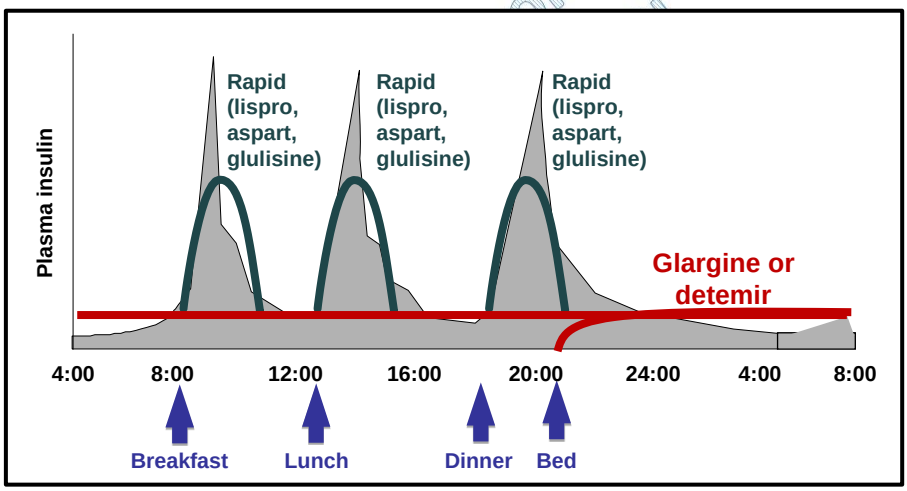
47

Pharmacokinetics of Insulin Products



48

Basal/Bolus Treatment Program With Rapid-Acting and Long-Acting Analogs



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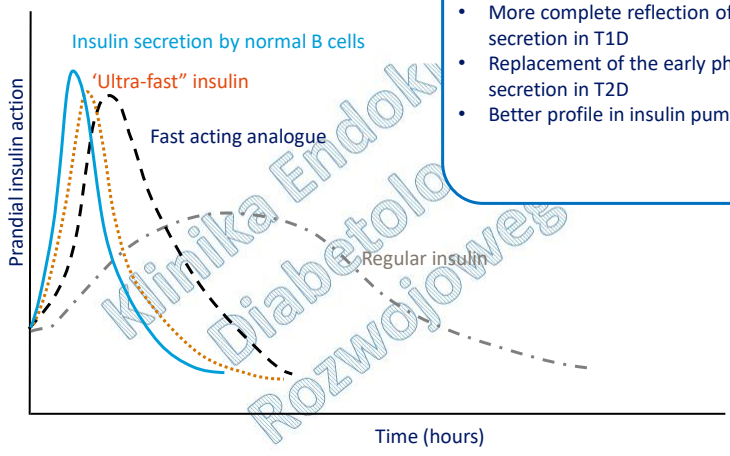
Ultra-fast acting prandial insulin



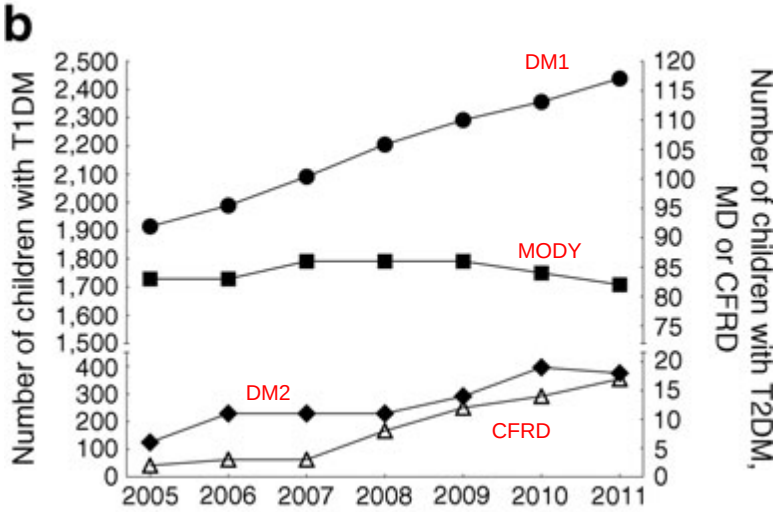
Ultra-fast insulin:
- More complete reflection of insulin secretion in T1D
- Replacement of the early phase of insulin secretion in T2D
- Better profile in insulin pump therapy

Home. Diabetes Obes Metab 2015;17:1011–20

50

DM EPIDEMIOLOGY IN POLAND

W. Fendler i wsp. Diabetologia (2012) 55:2631–2635



51

Diabetes mellitus is a chronic systemic diseases with hyperglycemia due to:

a. insulin deficiency
b. deficiency of glukagon
c. insulin resistance
d. insuffiecency of adrenal glands

The true answer is:

1. a,c
2. a,b
3. d,c
4. a,d

52

The symptoms of ketosis in diabetes mellitus are (match all true answers):

a. nausea, vomiting, abdominal pain, dehydration of body

b. vomiting, abdominal pain, dyspepsia

c. cardiac pain, vomiting, Kussmaul respiration

d. Kussmaul respiration, nausea, an acetone odor to the breath

53

The treatment of ketoacidosis consist of:

a. infusion of regular insulin, fluid, potassium and close monitoring of vital signs.

b. infusion of regular insulin, bicarbonate and fluid

c. infusion of fluid and close monitoring of vital signs.

d. infusion of insulin and bicarbonate.

54

Agenda:

1. Diabetes: diagnosis, DKA and hypoglycemia
2. Adrenals: Addisonian crisis, CAH
3. Thyroid gland: hypothyroidism, hyperthyroidism
4. Pubertal timetable & tricks
5. Growth

55

Adrenal gland disorders

- Hypofunction
  - Addison's disease (AD)
  - Hypoaldosteronism
- Hyperfunction
  - Cushing's disease/syndrome (C's)
  - Excess androgen secretion
  - Excess estrogen sectretion
- Adrenal enzyme deficiencies
  - Congenital adrenal hyperplasia (CAH)

56

Adrenal insufficiency

- Primary / Secondary
  - Primary: lesion of the adrenal glands themselves
  - Secondary: inadequate secretion of ACTH by the pituitary gland
- Acute / Chronic
- Isolated / Polyendocrine deficiency syndrome

57

Primary adrenal insufficiency - etiology

Hereditary

- CAH
- C.A.Hypoplasia (X-linked and AR)
- Adrenal unresponsiveness to ACTH
- Adrenoleukodystrophy
- Adrenomyeloneuropathy
- Refsum disease
- Wolman disease

Autoimmune

- AD
- Polyglandular autoimmune syndromes type 1 and 2

Infectious:

- TBC
- Fungal
- HIV
- CMV

Other:

- Adrenal hemorrhage
- Triple A syndrome (adrenal insufficiency, alacrimia, achalasia)
- Medications: ketoconasole (decreased steroid synthesis), increased steroid metabolism (e.g. phenobarbital)

58

Secondary adrenal insufficiency

- ACTH deficiency
- Panhypopituitarism
- Hypothalamic/pituitary disorders (tu, surgery, rth)
- Withdrawal from glucocorticoid therapy
- Inadequate glucocorticoid replacement (Infection, surgery, stress)
- Infant born from steroid-treaeted mother

59

Adrenal enzyme deficiencies

- CAH
- Congenital lipoid adrenal hyperplasia

60

Addison's disease

- Addison's disease is a rare endocrine disorder (1:100000, autoimmune destruction of adrenals) that occurs when the adrenal glands do not produce enough **cortisol**
- Synonyms: chronic adrenal insufficiency, or hypocortisolism
- Occurs in all age groups
- **M=F**
- Often positive adrenal antibodies
- Occurs when app. 90% of adrenal cortex has been destroyed

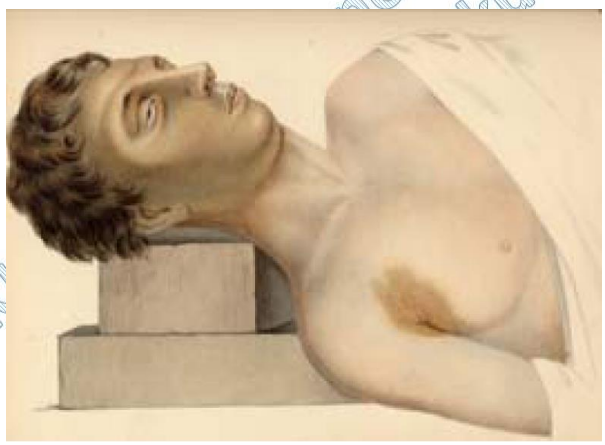
61

Addison's disease: Symptoms

- Fatigue
- Muscle weakness
- Fasting hypoglycemia
- Nausea, vomitting, diarrhea
- Weight loss
- Low blood pressure
- Pigmentation of the skin (exposed and non-exposed parts of the body)
- HYPOTENSION→SHOCK→DEATH

62

Addison's disease



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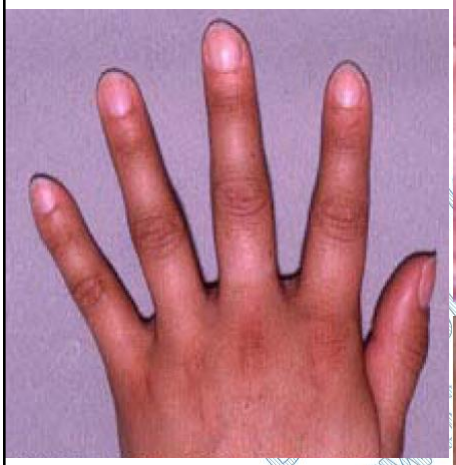

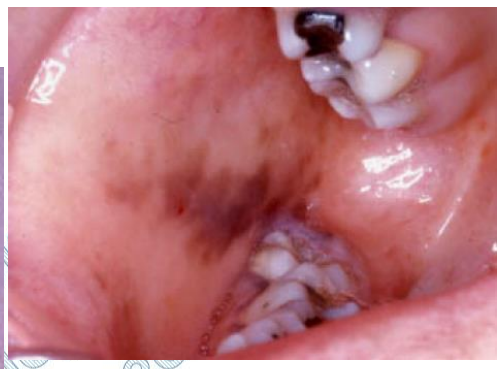

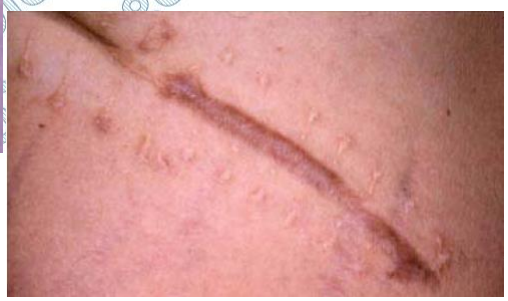

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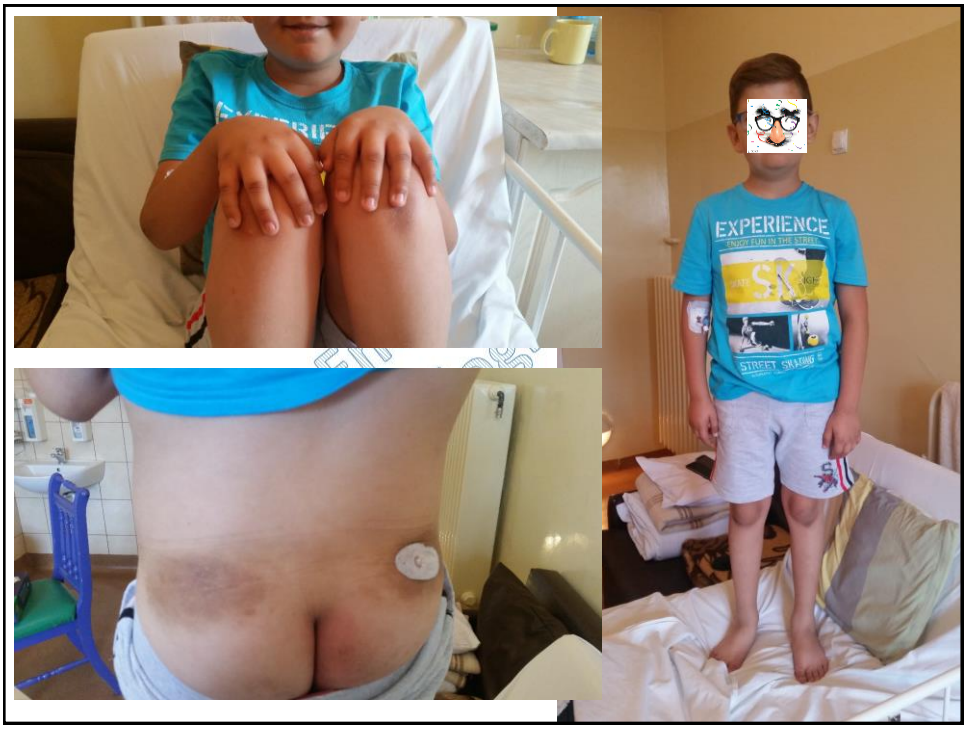


65

ADDISONIAN/Adrenal CRISIS

Clinical

- Sudden, penetrating pain in the lower back, abdomen, legs
- Severe vomiting and diarrhoea with dehydratation
- Low blood pressure and shock
- Hypoglycemia
- Lost of consciousness
- FATAL, if untreated

Lab workout

- **Low Na, high K**
- Elevated urea/BUN due to dehydratation
- **Hypoglycemia**
- Anemia and eosinophilia
- Elevated renin and **ACTH** plasma levels
- **Low cortisol**

66

Treatment

- **HYDROCORTISONE i.v. 1-2 mg/kg in bolus plus 4-10 mg/kg/day in 3-4 doses (i.v.)**
- **Na^+ replacement** (rehydration, do not administrate fluids with K^+)
- Acidosis treatment
- Aldosterone, DOCA if needed

67

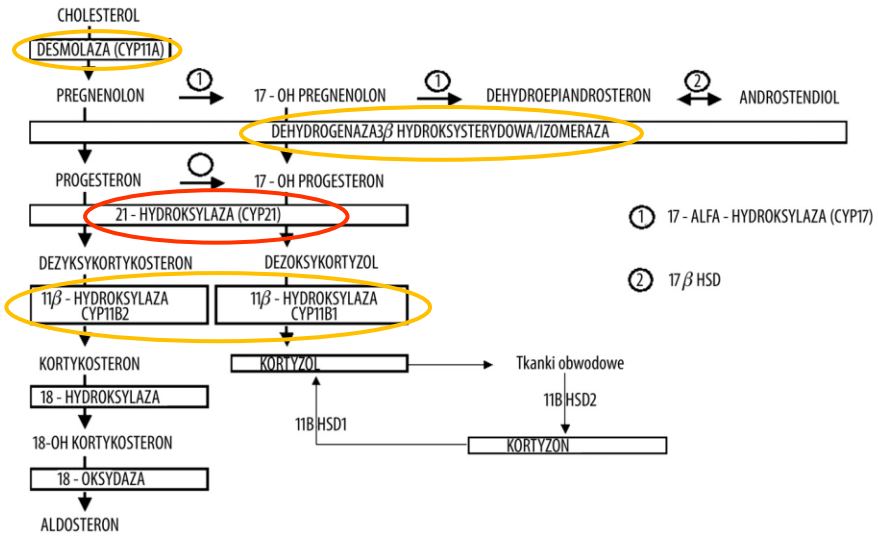
Congenital adrenal hyperplasia (CAH)

- Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders of cortisol biosynthesis.
- **Cortisol deficiency increases secretion (ACTH), leading to adrenocortical hyperplasia and overproduction of intermediate metabolites.**
- Depending on the enzymatic step that is deficient, there may be signs, symptoms, and laboratory findings of:
  - **Mineralocorticoid deficiency or excess**
  - **Incomplete virilization or premature puberty in affected males**
  - **Virilization or sexual infantilism in affected females**

68

Adrenal Cortex: Steroid Hormone Production

(Helmberg, New, Romer])



69

CAH

- More than 90% of CAH cases are caused by 21-hydroxylase deficiency -this P450 enzyme hydroxylates progesterone and 17-hydroxyprogesterone, affects synthesis of aldosterone and cortisol.
- ***Classic* 21-hydroxylase deficiency** (1:15000-20000)**:**
  - Both hormones are deficient in the most severe, „*salt wasting*" form of the disease. 75%
  - Slightly less severely affected patients are able to synthesize adequate amounts of aldosterone but have elevated levels of androgens of adrenal origin; „*simple virilizing*" disease. 25%
- Patients with ***nonclassic* disease** have relatively mildly elevated levels of androgens and may have signs of androgen excess postnatally. (1:1000)

70

ALDOSTERONE AND CORTISOL DEFICIENCY:

- „Salt wasting" form classic 21-hydroxylase deficiency:
- Symptoms:
  - Progressive weight loss, anorexia, vomiting, dehydration, weakness, hypotension, hypoglycemia, hyponatremia and hyperkalemia.
  - **Develop in affected infants at approximately 2 wk of age.**
  - Without treatment, shock, cardiac arrhythmias, and death may occur within days or weeks.

71

„Salt wasting" form

- Cortisol is not synthesized efficiently ⇨ ACTH levels are high ⇨ hyperplasia of the adrenal cortex and ↑ levels of precursor steroids (that may be 100xnormal)
- Precursors include **17-hydroxyprogesterone and progesterone.**
- Progesterone act as antagonist of the mineralocorticoid receptor and thus may exacerbate the effects of aldosterone deficiency in untreated patients.

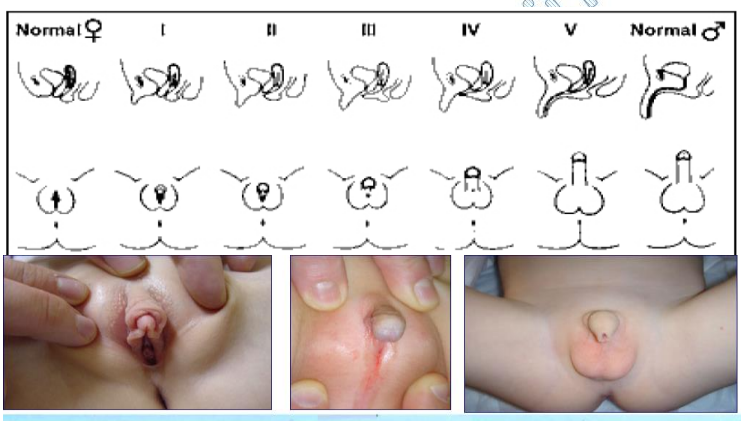
72

Androgen excess prenatally:

- Accumulation of steroid precursors is that 17-OH-P is shunted into the pathway for androgen biosynthesis, ⇨high levels of androstenedione that are converted outside the adrenal gland to testosterone.
- **Begins by 8–10 wk of gestation and leads to abnormal genital development in females.**
- Affected females, who are exposed in utero to high levels of androgens of adrenal origin, have masculinized external genitalia.
  - Enlargement of the clitoris (resembles a penis).
  - Partial or complete labial fusion.
  - Vagina usually has a common opening with the urethra (urogenital sinus).
  - Because the urethra opens below the *penis*, some affected females may be mistakenly presumed to be males with hypospadias and cryptorchidism.
  - The internal genital organs are normal, because affected females have normal ovaries and not testes
  - Prenatal exposure of the brain to high levels of androgens may influence subsequent sexually dimorphic behaviors in affected females
- **Male infants appear normal at birth.**
- The diagnosis may not be made in boys until signs of adrenal insufficiency develop.

73

The Prader's scale



	1	2	3	4	5
Hbd	20	16	14	12	10

74

POSTNATAL ANDROGEN EXCESS

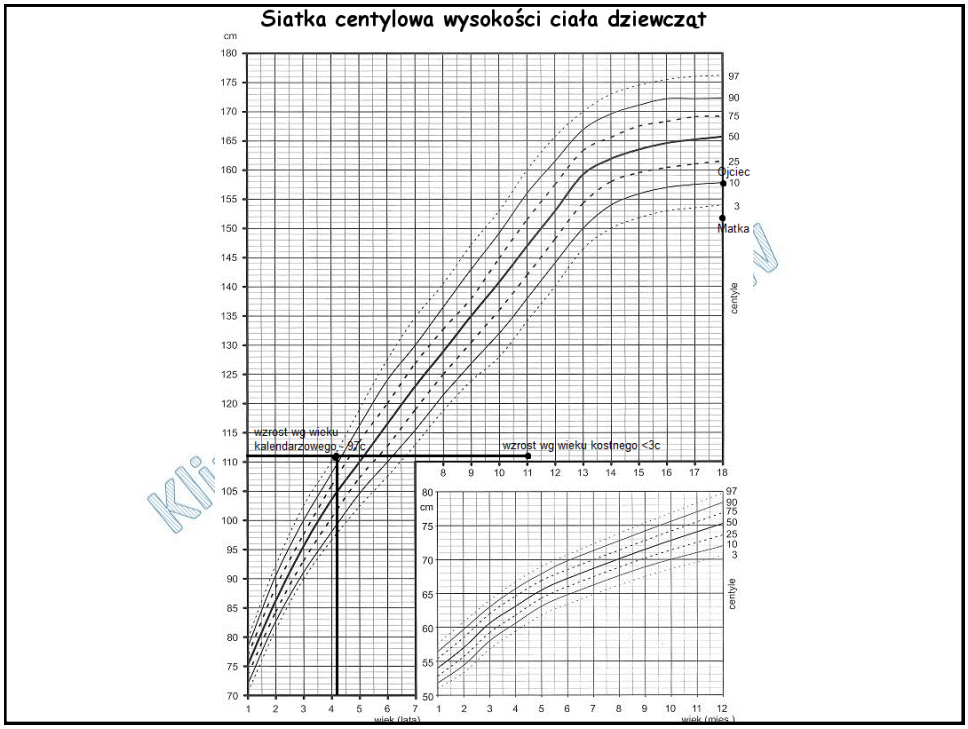
- Untreated or inadequately treated children of both sexes develop additional signs of androgen excess after birth.
- Boys with the simple virilizing form appear normal and rarely develop adrenal insufficiency (delayed diagnosis).
- **Signs of androgen excess include rapid somatic growth and accelerated skeletal maturation**.
- Affected patients are tall in childhood but premature closure of the epiphyses causes growth to stop relatively early, and adult stature is stunted

75

POSTNATAL ANDROGEN EXCESS

- Muscular development may be excessive.
- Pubic and axillary hair
- acne
- deep voice
- The penis, scrotum, and prostate may become enlarged in affected boys
- The testes are usually prepubertal in size [appear relatively small in contrast to the enlarged penis].
- The clitoris may become further enlarged.
- Although the internal genital structures are female, breast development and menstruation do not occur unless the excessive production of androgens is suppressed by adequate treatmen

76



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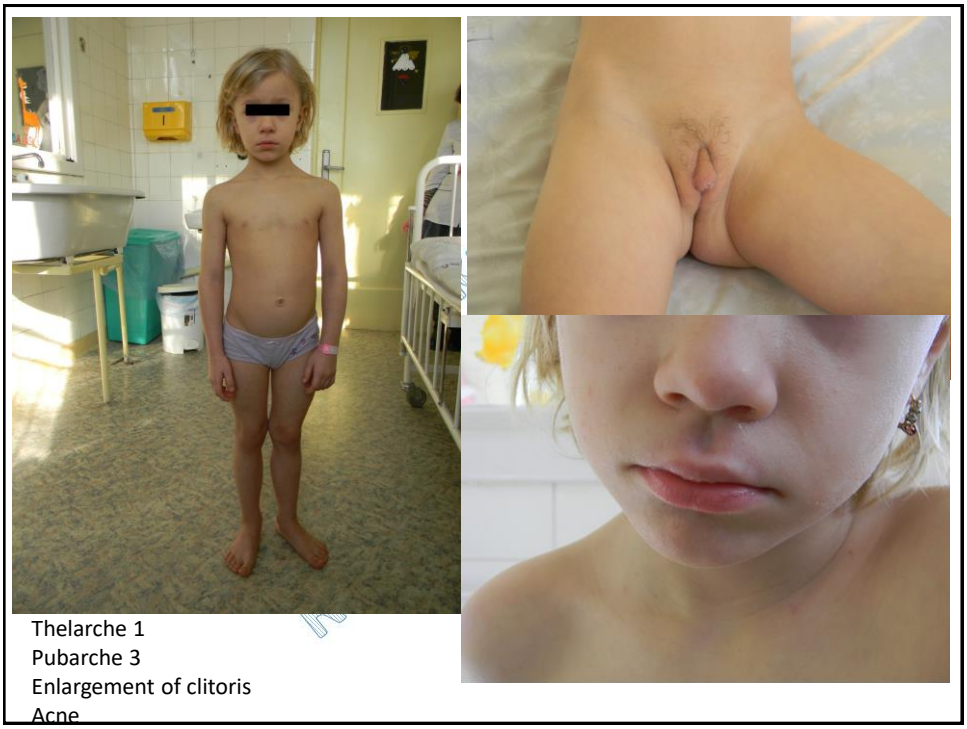


Thelarche 1
Pubarche 3
Enlargement of clitoris
Acne

78

Nonclassic 21-hydroxylase deficiency

- **Similar but milder signs of androgen excess**
- Cortisol and aldosterone levels are normal and affected females have normal genitalia at birth.
- Males and females may present with precocious pubarche.
- Hirsutism, acne, menstrual disorders, and infertility may develop.
- Many females and males are completely asymptomatic
- M=F

79

Diagnosis:

- Salt losing disease: Typical findings of cortisol and aldosterone deficiency: **hyponatremia, hyperkalemia, acidosis, and often hypoglycemia**. (1–2 wk or longer to develop after birth).
- **17-hydroxyprogesterone are elevated**.
- Cortisol levels are low in patients with the salt-losing type of disease. They are often normal in pts with the simple virilizing type but inappropriately low in relation to the ACTH and 17-hydroxyprogesterone levels.
- Androstenedione and testosterone are elevated in affected females.
- Testosterone is not elevated in affected males because normal infant males have high testosterone levels compared with those seen later in childhood.
- Levels of urinary 17-ketosteroids and pregnanetriol are elevated.
- Plasma levels of renin are elevated, and serum aldosterone is inappropriately low for the renin level.

80

DHEA-S04 µg/dl	Estradiol pg/ml	FSH mIU/ml	LH mIU/ml	Testosteron ng/ml	Androstendion ng/ml	17-OH progesteron ug/dl
132 Norma 35-430	<20 Norma < 30	1,4 Norma 0,11-1,6	<0,1 Norma <1,3	2,91 Norma 0,2-0,73	> 10,0 Norma 0,3- 3,3	45,9/ 44,2 Norma 3-5 lat 0,64

	7:00	14:00	20:00
Kortyzol (µg/dl) (N: 3,7-19,4 (do 10:00); 2,9-17,3 (po 17:00)	4,2	8,3	3,7
ACTH (pg/ml) (N: do 46,0)	654,0	234,0	217,0

Na [mmol/l]	K [mmol/l]
143 / 138 Norma-135- 146	5,05 /5,02 Norma- 3,5- 5,1

81

Treatment:

- **Cortisol deficiency is treated with glucocorticoids.**
- Treatment also suppresses excessive production of androgens by the adrenal cortex .
- Double or triple doses are indicated during periods of stress, such as infection or surgery.
- Glucocorticoid treatment must be continued indefinitely in all patients with classic 21-hydroxylase deficiency but may not be necessary in patients with nonclassic disease unless signs of androgen excess are present.
- **Patients with salt-wasting disease require mineralocorticoid replacement with fludrocortisone**

82

Agenda:

1. Diabetes: diagnosis, DKA and hypoglycemia
2. Adrenals: Addisonian crisis, CAH
3. Thyroid gland: Hypothyroidism, hyperthyroidism
4. Puberty: metabole & tricks
5. Growth

83

TH control

TRH

- Produced by hypothalamus
- Release is pulsatile and circadian
- Downregulated by T3
- Travels through portal venous system to adenohypophysis
- Stimulates TSH production

TSH

- Produced by adenohypophysis thyrotrophs
- Upregulated by TRH
- Downregulated by T4 and T3
- Travels through portal venous system to cavernous sinus and body
- Stimulates:
  - Iodine uptake
  - Colloid endocytosis
  - Growth of thyroid gland

84

TH

- Majority of circulating hormone is T4 (98,5% vs 1,5%)
- Total hormone load is influenced by serum binding proteins
  - Albumin 15%
  - Thyroid binding globulin 70%
  - Transthyretin 10%
  - Others 5%
- Regulation is based on the free component of thyroid hormone

85

Effects of Thyroid Hormone

- Fetal brain and skeletal maturation
- Increase in basal metabolic rate
- Inotropic and chronotropic effects on heart
- Increases sensitivity to catecholamines
- Stimulates gut motility
- Increase bone turnover
- Increase in serum glucose, decrease in serum cholesterol

86

Thyroid Function Testing

- **TSH**
- Total (historical) and **free T4**
- Total (historical) and **free T3**
- T3 resin uptake (T3RU) (Historical)
- Reverse T3 (Historical)
- **Thyroglobulin**

87

Thyroid Testing

- **TSH**
  - **Best test for screening for thyroid dysfunction!**
  - Log/linear response w/ FT4
    - A 2-fold change in FT4 produces a 100-fold change in TSH
  - Not specific for a particular thyroid disease.
    - Don't use TSH alone for diagnosis!
  - Also useful in
    - Assessing LT4 tx in 1° hypothyroidism
    - Monitoring TSH-suppressive tx in thyroid Ca

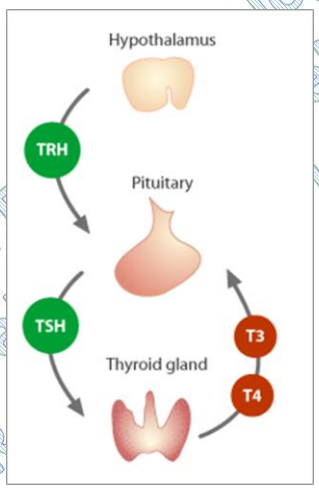
88

Thyroid Testing

- **FT4**
  - Testing methods:
    - Equilibrium dialysis
    - Analog assays
  - **If abnormal TSH - check FT4 next**
  - Indications:
    - In conjunction w/ TSH for diagnosing hyperthyroidism or hypothyroidism.
    - **Monitoring LT4 replacement in central hypothyroidism (TSH not helpful)**
    - Assessing response to tx following 131-RAIA (Graves, toxic nodules)
- **FT3**
  - **Abnormal TSH + normal FT4, then check this one** (T3 Thyrotoxicosis)
  - In Hyperthyroidism

89

Negative feedback loop



90

Thyroid Testing

- **Thyroid Antibodies (TPO, Tg, TRAb)**
  - TPO
    - TPO + Tg Ab's assoc w/ **Hashimoto's.** TPO more sensitive.
    - Helpful in predicting those w/ subclinical hypothyroidism who are at ↑ risk for progression to overt hypothyroidism.
  - TRAb
    - When dx of **Graves'** in question
      - Note: a negative test does not r/o Graves'
    - Pregnant women w/ Graves'
      - to determine fetal risk of thyroid dysfunction (due to transplacental passage of stimulating or blocking Ab's).
    - Suspected euthyroid ophthalmopathy.
    - In pt's w/ alternating hyper- and hypothyroidism (due to fluctuations in TSH receptor stimulating and blocking and stimulating Ab's)
- **Thyroglobulin (Tg)**
  - Indications
    - **Thyroid cancer** recurrence
    - Factitious (exogenous) vs. endogenous hyperthyroidism
  - Note: Most assays are not reliable in pt's (+) for anti-Tg Ab
    - Interferes w/ method of Tg measurement (causing factitious low Tg)

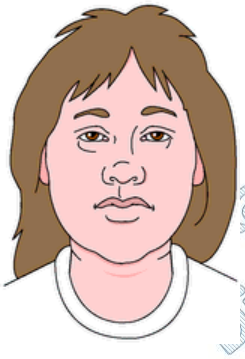
91

Overview of Thyroid Function Tests

TSH	FT4	Clinical Status
HIGH	LOW	Primary Hypothyroidism, Thyroiditis (stage 3)
	NORMAL	Subclinical Hypothyroidism
	HIGH	Pituitary Hyperthyroidism
LOW	HIGH	Thyrotoxicosis, Thyroiditis (stage 1)
	NORMAL	Subclinical Hyperthyroidism, Autonomous nodules
	LOW	Pituitary Hypothyroidism

92

Hypothyroidism



- Symptoms
  - General Slowing Down
  - Lethargy/somnolence
  - Depression
  - Modest Weight Gain
  - Cold Intolerance
  - Hoarseness
  - Dry skin
  - Constipation (↓ peristaltic activity)
  - General Aches/Pains
    - Arthralgias or myalgias (worsened by cold temps)
  - Brittle Hair
  - Menstrual irregularities
    - Excessive bleeding
    - Failure of ovulation
  - ↓ Libido

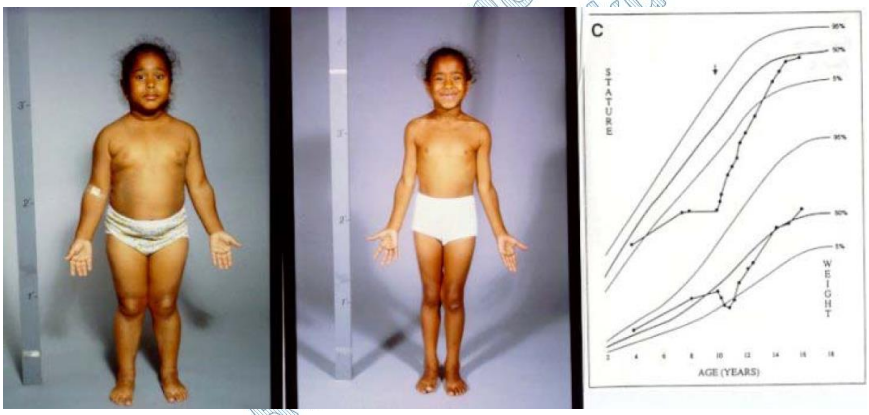
93

Symtoms and signs

Congenital Hypothyroidism	Acquired Hypothyroidism
Findings During the First 2 Postnatal Weeks • Prolonged neonatal jaundice • Edema of the eyelids, hands, and feet • Gestation >42 wk • Birthweight >4 kg • Poor feeding • Hypothermia • Protuberant abdomen • Large anterior and posterior fontanelles *Findings Beyond Age 1 Month* • Darkened and mottled skin • Stressful, frequent, and labored breathing • Failure to gain weight; poor sucking ability • Decreased stool frequency • Decreased activity and lethargy *Findings After Age 3 Months* • Umbilical hernia • Infrequent and hard stools • Dry skin with carotenemia • Macroglossia • Generalized swelling or myxedema • Hoarse cry	*Findings Between 6 Months and 3 Years of Age* • Deceleration of linear growth • Coarse facial features • Dry skin with carotenemia • Hoarse cry and large tongue • Umbilical hernia • Muscular pseudohypertrophy (enlargement of the arm and leg muscles) *Findings During Childhood* • Deceleration of linear growth with or without short stature • Delay in eruption of teeth and in shedding of primary teeth • Muscle weakness and pseudohypertrophy (enlargement of the arm and leg muscles) • Infrequent and hard stools • Dry skin with carotenemia • Generalized swelling or myxedema • Precocious sexual development: breast development without sexual hair in girls; enlarged testes without sexual hair in boys *Findings During Adolescence* • Delayed onset of puberty • Deceleration of linear growth with or without short stature • Delay in eruption of teeth and in shedding of primary teeth • Infrequent and hard stools • Dry skin with carotenemia • Galactorrhea (girls) • Generalized swelling or myxedema

94

Short stature, obesity



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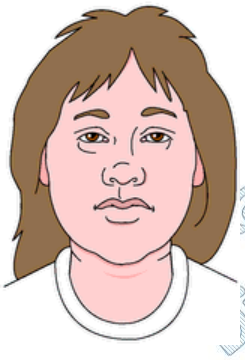
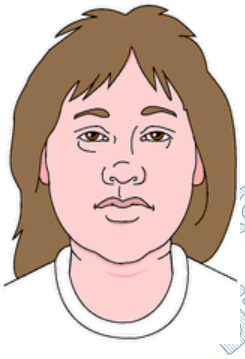
Hypothyroidism



- Exam:
  - Dry, pale, course skin w/ yellowish tinge
  - Periorbital edema
  - Puffy face and extremities
  - Sinus Bradycardia
  - Diastolic HTN
  - ↓ Body Temperature
  - Delayed relaxation of DTRs
  - Megacolon (↓ peristaltic activity)
  - Pericardial/ pleural effusions
  - CHF
  - Myxedema (nonpitting edema)
- Bradycardia and hypothermia- think hypothyroidism!

96

Hypothyroidism



- Laboratory Findings
  - Elevated TSH
  - Low FT4
  - TPO Ab (+)
    - Pregnant women w/ TPO Ab (+)
      - Miscarriage rate doubles
      - ↑ risk post partum thyroiditis (35%)
  - mild anemia
  - ↑ CPK-MB
  - ↑ LDL, ↑ Chol (↓ lipid clearance)
  - Hyponatremia

97

Hypothyroidism (Treatment)

LT4

- **Initial starting dosage 1.6 mg/kg/day.**
  - Dose correlates better w/ lean body wt
- ≈ 80% of PO dose of LT4 is absorbed
- The main absorptive sites proximal and mid-jejunum.
- **Food can ↓ LT4 absorption up to 40-50%.**
- Serum LT4 levels rise 10-15% after ingestion, peaking at 2-4 hrs.
  - Serum LT3 levels don't change due to the slow peripheral conversion of T4 → T3.
- T-1/2 LT4 is 7 days
  - can be given weekly in non compliant pt's.
- Goal LT4 replacement: TSH 1.0-2.5 mU/L

98

Hypothyroidism (treatment in general)

Indications for LT4 replacement

- Asymptomatic: TSH > 10
- Asymptomatic and TPO Ab (+): TSH > 5
- Symptomatic: TSH > 5
- Pregnant female: TSH > 2.5
- Goitrous: TSH > 5

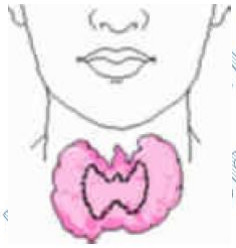
99

Hashimoto disease

- The most common cause of acquired hypothyroidism
- F:M 3:1
- In children – mostly asymptomatic goiter, or symptoms nonspecific
- More frequent in Down and Turner Syndromes

100

Goiter



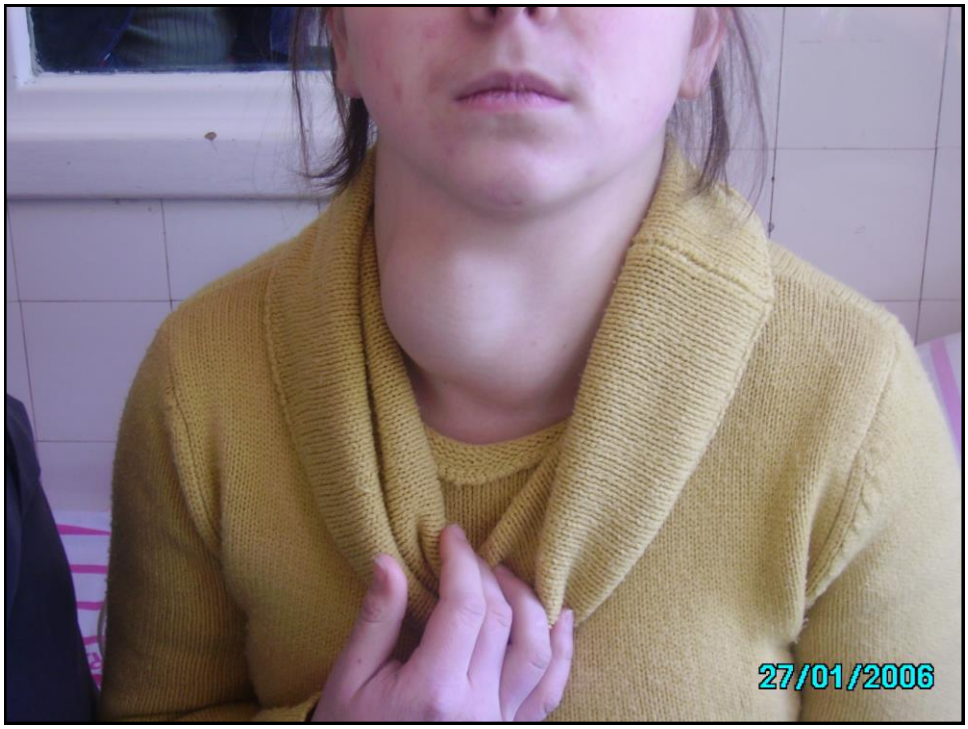
- Chronic enlargement of the thyroid gland

101

WHO classification

- Grade 0 – no goiter presence is found
- Grade 1 – neck thickening is present in result of enlarged thyroid, palpable, however not visible in normal position of the neck. The thickened mass moving upwards during swallowing. Grade 1 includes also nodular goiter if thyroid enlargement remans invisible.
- Grade 2 – neck swelling visible if neck is in normal possition, corresponding with enlarged thyroid found in palpation.

102



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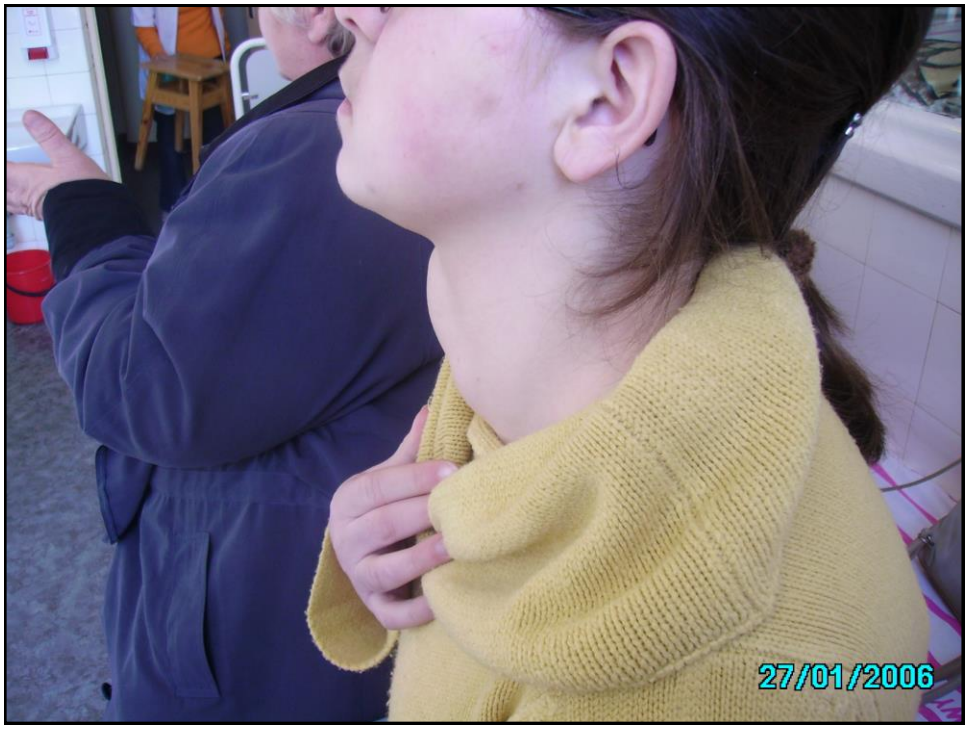

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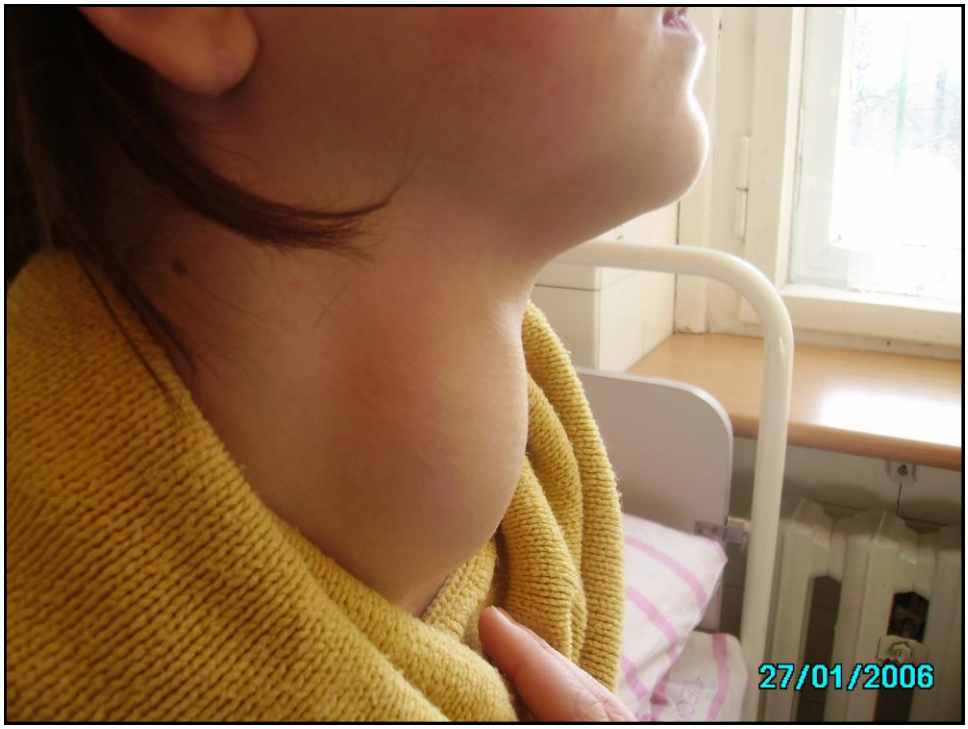
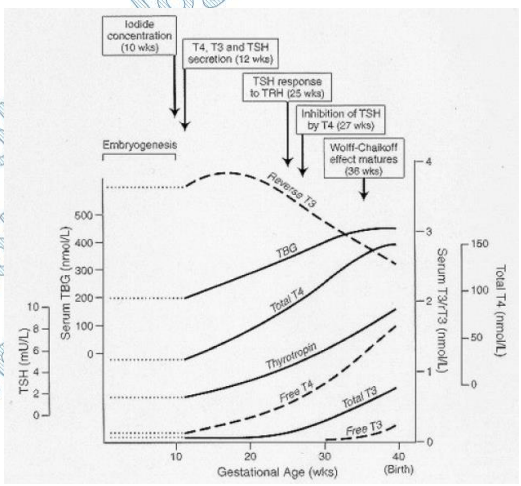


105

Thyroid maturation in fetus

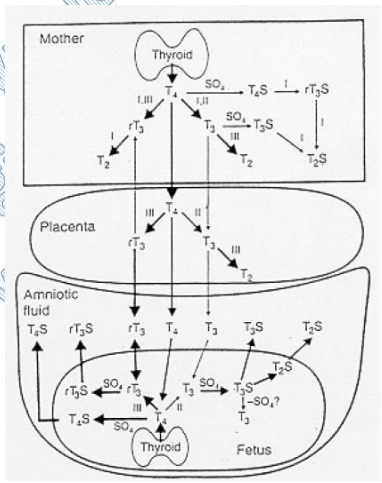
- „Fetal” TSH is detectable by 12 Hbd
- Negative feedback mechanisms are established by 20 Hbd
- rT3 concentration is high
  (rT3=reverse T3)



106

Mother – foetus relation

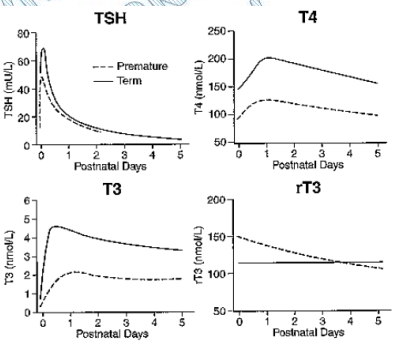
- **Fetal hormonal axis is independent**
  - Limited T4 exchange
  - Placental type 3 deiodonase
- Effect of maternal hypothyroidism is most important in the first trimester
- **Placenta is permeable to TRH, IgG and thionamides**



107

Changes at birth

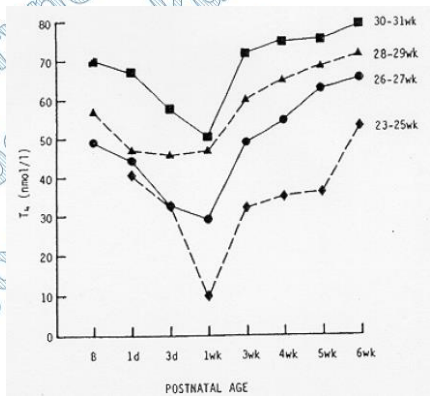
- There is a surge of TSH, T3 and T4 at birth, that is important for screen results.
- Lower rise is observed in preterms – preterms should have TSH and fT4 checked again.



108

Thyroid status in preterms

- Immaturity of axis
- Nadir at 2-3 weeks
- Influences:
  - Illness
  - Iodine exposure and stores
  - T4 clearance
- **TSH not elevated**



110

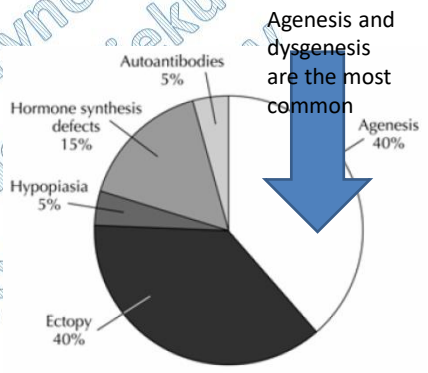
Congenital Hypothyroidism

- Incidence ratio **1:4000**
  - **Higher in F**
  - Higher in Asian
  - Lower in Black
- Primarily sporadic occurance
- **Overt symptoms may not be present at birth**
- **Profoud effects on CNS development, but no sequelae if treatment initiated by 2-4 weeks (10-15mcg/kg/day)**
- Reliable testing and SCREENing available (TSH and/or fT4, in Poland - TSH)

111

Etiology of Primary Congenital Hypothyroidism

- Known precise etiology does not change immediate treatment plans, therefore extensive testing is usually not necessary.
- However, it may be helpful in assessment of risk in future pregnancies and may allow early determination od transient vs permanent disease.



112

Trancient CH

- Abnormal newborn screen with abnormal confirmatory lab. Results
  - 75-80% of abnormal screens due to false +
- Incidence estimated – **10%** of all cases
- Most common in premature babies
- Causes:
  - Iodine deficiency or excess
  - Maternal antithyroid medication
  - Maternal TSH receptor blocking antibodies

113

Treatment

- Confirm all abnormal newborn screens with lab. TSH and fT4. Borderline results require retesting in 2-4 weeks.
- If lab. results are abnormal, begin **THYROXINE 10-15mcg/kg/day** (usually 25-37 mcg/day). The goal is to start the therapy within the first month, **optimal – 2 weeks**.
- Follow up in 2-3 months to adjust the dose.
- If no need to increase the dose by 2-3 years, give 4 weeks off of thyroxine for diagnosis verification.

114

Hyperthyroidism

- Thyrotoxicosis = "any condition that results in thyroid hormone excess"
  - Includes: Graves Disease, Toxic Goiter, Thyroiditis, and Excessive Thyroxine Ingestion
- Hyperthyroidism = "Specifically hyperfunctioning of the thyroid gland"
  - Most Commonly caused by Graves Disease in the young
  - Toxic Nodular Goiter in the elderly

115

Hyperthyroidism

- Graves Disease (>95% of Cases)
  - Relatively rare in children
  - Incidence increases with puberty
  - Female:Male (3-5:1)
- Neonatal Graves
  - Transplacental Antibodies
- Hashitoxicosis
- TSH receptor mutations (gain of function)
  - McCune Albright syndrome
- Subacute Thyroiditis
- Exogenous thyroxine Exposure

116

Hyperthyroidism

- Symptoms
  - Jittery, shaky, nervous
  - Difficulty concentrating
  - Emotional lability
  - Insomnia
  - Rapid HR, palpitations, DOE
  - Feeling Hot
  - Weight Loss (can see weight gain)
  - Freq BMs (hyperdefecation, not diarrhea)
  - Fatigue
  - Menses w/ lighter flow, shorter duration

117

Hyperthyroidism

- Exam
  - Eye findings (20%)
  - Goiter
  - Thyroid bruit or thrill
  - Tachycardia: Sinus Tach, A-Fib
  - Flow murmur
  - Systolic Hypertension
  - Hyperreflexia
  - Tremors
    - UE, tongue
  - Proximal muscle weakness
  - Thenar/ hypothenar atrophy
  - Acropachy
  - Onycholysis (<1%)
    - separation of nail from the nailbed
  - Dermopathy (1%)

118

Hyperthyroid Eye Disease

- Hyperthyroidism (any cause)
  - Lid lag, lid retraction and stare
  - Due to increased adrenergic tone stimulating the levator palpebral muscles.
- True Graves' Ophthalmopathy
  - Proptosis
  - Diplopia
  - Inflammatory changes
    - Conjunctival injection
    - Periorbital edema
    - Chemosis
  - Due to thyroid autoAb's that cross-react w/ Ag's in fibroblasts, adipocytes, + myocytes behind the eyes.

119

Graves' Disease

- **Most common form of thyrotoxicosis**
- Autoimmune etiology with familial predisposition
- Thyroid receptor stimulating antibody unique to Graves' disease; other autoantibodies present (TgAb, TPOAb)
- Affects females five times more often than males

120

Signs and symptoms in children

- Change in school performance
- Insomnia
- Restlessness, irritability
- Nocturia
- Bone age advancement
- Infants: premature birth, craniosynostosis, poor feeding, failure to thrive
- Weight loss, polyphagia, tachycardia, increased pulse and systolic pressure with decreased diastolic pressure, heat intolerance, diarrhea, tremor

121

Neonatal Grave's

- Rare < 2% infants born to Graves" moms
- **2 types:**

Transplacental trnsfr of TSH-R ab (IgG)

- Present at birth, self-limited
- Rx PTU, Lugol's, propanolol, prednisone
- Prevention: TSI in mom 2nd trimester, if 5X normal then Rx mom with PTU (crosses placenta to protect fetus) even if mom is euthyroid (can give mom LT4 which won't cross placenta)

Child develops own TSH-R ab

- Strong family hx of Grave's
- Present @ 3-6 mos
- 20% mortality, persistant brain dysfunction

122

Neonatal Hyperthyroidism

- Almost always transient
- Usually associated with maternal Graves
- Incidence 1:50 000 neonates, 1-2% mums with Graves
- Often presents in first week of life, emerging with clearence of maternal thionamide
- Treatment – PTU, methimazole, propranolol

123

Hyperthyroidism

- Laboratory Findings
  - TSH nearly undetectable
  - Elevated FT4 or FT3
  - mild leukopenia,
  - N/N anemia,
  - ↑ LFT's and alk phos,
  - mild ↑ Ca++,
  - ↓ albumin
  - ↓ chol

124

Hyperthyroidism (Treatment)

1) β-blockers (symptom control)
   - Propranolol : 60-320 mg daily
   - Atenolol : 50-100 mg daily
   - Metoprolol : 50-100 mg bid
   - If β-blocker contraindicated then Verapamil 40-80 mg tid
2) 131-RAIA (70% thyroidologists prefer)
   - Dosing
     - Graves: 10-15 mCi
     - Toxic MNG/Adenoma: 20-30 mCi
   - **Absolute contraindications**
     - **Pregnancy and nursing moms (excreted in breast milk)!**
   - Pregnancy should be deferred for at least 6 months following tx w/ 131-RAIA.
   - Prudent to avoid 131-RAIA in pt's w/ active moderate→ severe Graves' ophthalmopathy.

125

Hyperthyroidism (Treatment)

3) Antithyroid Drugs
- Propylthiouracil (PTU)
  - 100 mg bid-tid to start
- **Methimazole**
  - **10X more potent the PTU**
  - **10 mg bid-tid to start**
- Complications of ATD's
  - Dose dependent w/ Methimazole, Idiosyncratic w/ PTU.
  - **Agranulocytosis** (1/200-500)
    - usually presents w/ acute pharyngitis/ tonsilitis or pneumonia.
  - **Rash**
  - **Hepatic** necrosis w/ PTU, Cholestatic jaundice w/ Methimazole.
  - Arthralgias

126

Hyperthyroidism (Treatment)

3) Antithyroid Drugs
- **Candidates for ATD's**
  - **Children and adolescents**
  - Pt's w/ moderate→ severe ophthalmopathy
  - Thyroid Storm
  - Pt's w/ mild disease: small goiter, low titers of TSI (TSH-R Ab), low maintenance dose
  - Pt's w/ severe disease prior to 131-RAIA
    - stop ATD's 5-7 days prior to 131-RAIA
  - Labs
    - Follow TSH/FT4, CBC, LFT's

127

Hyperthyroidism (Treatment)

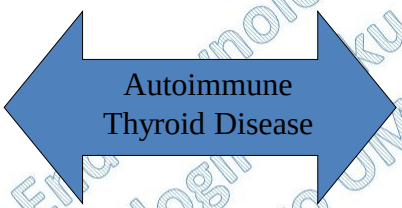
4) Surgery (sub-total thyroidectomy)
- Indications
  - Pt preference
  - Pregnant women w/ failed ATD's
  - Large or symptomatic goiters
  - When there is question of malignancy
- Need to be euthyroid prior to surgery
  - To ↓ the risk of arrhythmias during induction of anesthesia
  - To ↓ the risk of thyroid storm post operatively
  - ATD's + β-blockers
- Risks
  - Permanent hypoparathyroidism
  - Recurrent laryngeal nerve problems
  - Permanent hypothyroidism

128

TSH-R ab block

Thyroglobulin ab

Microsomal ab



TSH-R ab stim

Hashimoto's (hypothyroid)

Graves' Dx (hyperthyroid)

129

Autoimmune Polyglandular Syndromes 2

- Classic Triad:
  - Adrenal Insufficiency
  - Autoimmune thyroid disease (hypo or hyperthyroidism)
  - Type 1 DM
- Only 2 of the 3 are required for diagnosis
- F:M 3:1
- Age of onset tends to be between 20 and 30 years
- Other components of APS-2
  - Primary Hypogonadism
  - Myasthenia Gravis
  - Celiac disease
  - Pernicious Anemia
  - Alopecia
  - Vitiligo
  - Serositis
  - Stiffman Syndrome
  - ITP
  - IgA deficiency/ Goodpasture's syndrome

130

A Clinical Example

- 12 y.o. female referred for "abnormal thyroid function tests" and recent weight gain
- Locally: TSH = 6.2 mcIU/mL (0.35-4.94), free T4 = 1 ng/dL (0.7-1.5)
- Height points consistently at the 75th percentile
- PMH: Negative; Meds: None
- FH: No family history of thyroid disease
- Exam: No thyromegaly, otherwise normal, obesity

131

A Clinical Example

- Should this patient be started on thyroid replacement?
- If not, what is the next step?
- If thyroid functions should be repeated, when?
- Would thyroid antibodies be helpful?
- Any role for thyroid ultrasound?

132

Overview of Thyroid Function Tests

TSH	FT4	Clinical Status
HIGH	LOW	Primary Hypothyroidism, Thyroiditis (stage 3)
	NORMAL	Subclinical Hypothyroidism
	HIGH	Pituitary Hyperthyroidism
LOW	HIGH	Thyrotoxicosis, Thyroiditis (stage 1)
	NORMAL	Subclinical Hyperthyroidism, Autonomous nodules
	LOW	Pituitary Hypothyroidism

133

Agenda:

1. Diabetes: diagnosis, DKA and hypoglycemia
2. Adrenals: Addisonian crisis
3. Thyroid gland: hypothyroidism, hyperthyroidism
4. Puberty timetable & tricks
5. Growth

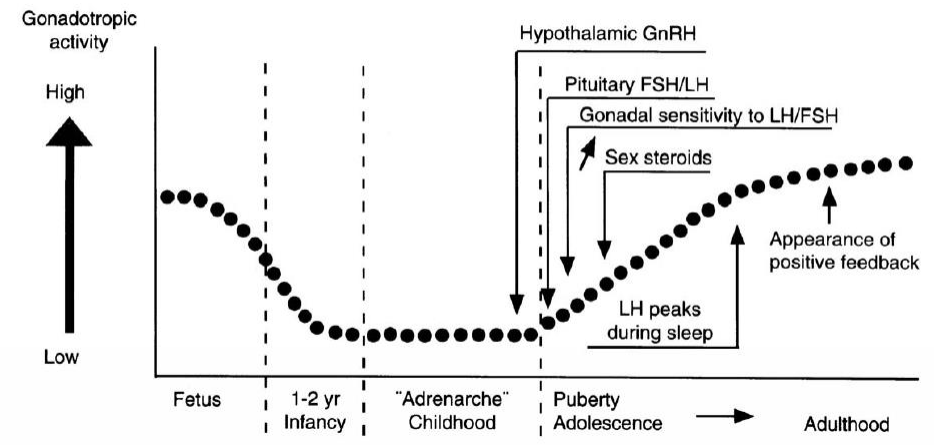
139

Physiology of puberty

- Puberty is the stage of physical maturation in which an individual becomes physiologically capable of sexual reproduction (manifested by spermatogenesis in the male and ovulation in the female).
- It lasts usually 2 to 5 years.

140

Activation of the hypothalamo-pituitary-gonadal axis



141

Puberty milestones

Female

- Thelarche- the onset of pubertal brest development
- Menarche- the onset of menstrual periods
- Pubarche - the onset of pubic hair development
- Growth spurt

Male

- Testes and penis growth
- Pubarche
- Spermarche
- Body and facial hair
- Voice change
- Growth spurt

142

Puberty – normal range

Girls

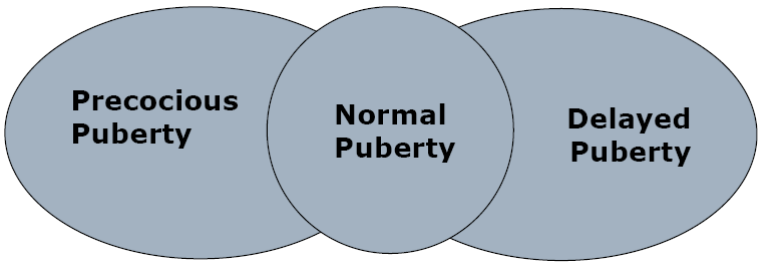
- Breasts – 8-13 yrs
- Pubic hair – 11,5 yrs
- Menarche – 12,9 yrs
- Growth spurt early
- Tanner V ~ 14 yrs
- Tempo – 2 yrs (0,5-4 yrs) (B→M)

Boys

- ↑ testes (>4ml) 9-14 yrs (11,2 yrs)
- Pubic hair – 12 yrs
- Growth spurt later
- Tanner V ~ 16 yrs
- Tempo – 1 genitalia stage 1-1,5yrs

143

Timing of the puberty



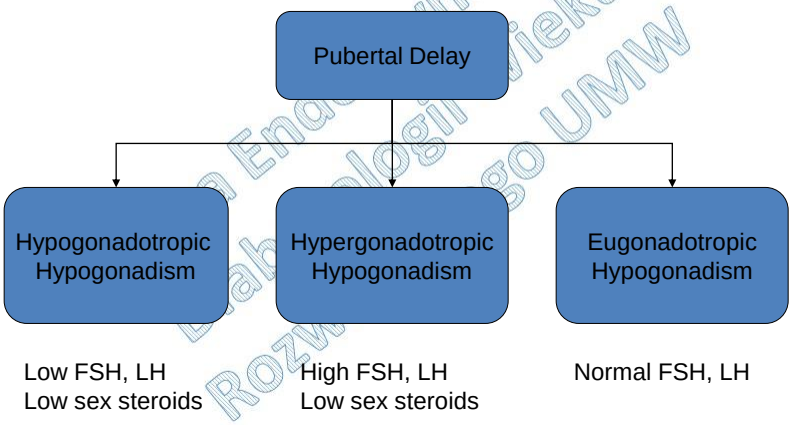
144

Timing of Puberty

- Consider **pubertal delay** if:
  - No breast development by age 13 in a female
  - No menses by age 15 in a female
  - Testicular size < 2.5cm or 4mL or pubic hair is not present by age 14 in a male
- Consider **precocious puberty** if:
  - Girls - Breast development before age 8 or menarche before age 10 in females
  - Boys - Testes volume > 3ml before 9 years.
  - Pubic hair development before 8 years in females, and 9 years in males

145

Pubertal Delay



146

Pubertal Delay

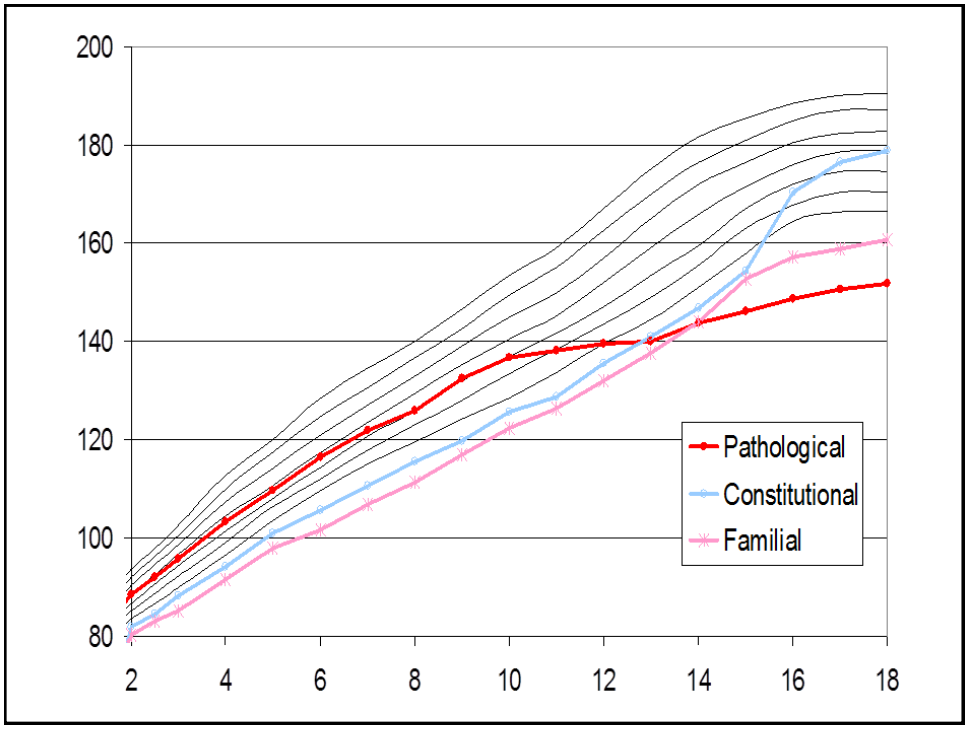
- Sedlmeyer et al. identified in their study that delayed puberty in men could be classified as
  - **Constitutional delay of growth & puberty in 63%**
  - Delay associated with underlying medical condition 20%
  - Hypogonadotropic hypogonadism 9%
  - Hypergonadotropic hypogonadism 7%

147

Hypogonadotropic **Hypo**gonadism

- Constitutional Delay of Puberty
- Malnutrition
- Excessive Exercise
- Growth Hormone Deficiency
- Isolated Gonadotropin Deficiency
- Endocrine Causes
- Miscellaneous syndrome complexes
- Brain tumors
  - Craniopharyngioma, astrocytomas, gliomas, histiocytosis X, germinomas, prolactinomas
- Iron overload (pituitary damage)
- GnRH receptor abnormalities

148



149

Kallman Syndrome

- A syndrome of **isolated gonadotropin deficiency**
- 1/10,000 males, 1/50,000 females
- **Present with ANOSMIA or HYPOSMIA**
- Can be difficult to differentiate from constitutional delay
- KAL-1 gene encodes protein (anosmin) required for GnRH neurons to migrate from olfactory placode to cribiform plate
- Can also be associated with harelip, cleft palate, and congenital deafness

150

Excessive exercise

- Questions as to whether lack of puberty related to low body weight or more as a direct effect of exercise
  - Interruption of training in ballet dancers, runners

151

Syndromes Associated with Pubertal Delay

- Prader-Willi syndrome
- Laurence Moon syndrome
- Septo-optic dysplasia
- Bardet-Biedl syndrome

152

Hypergonadotropic **hypo**gonadism

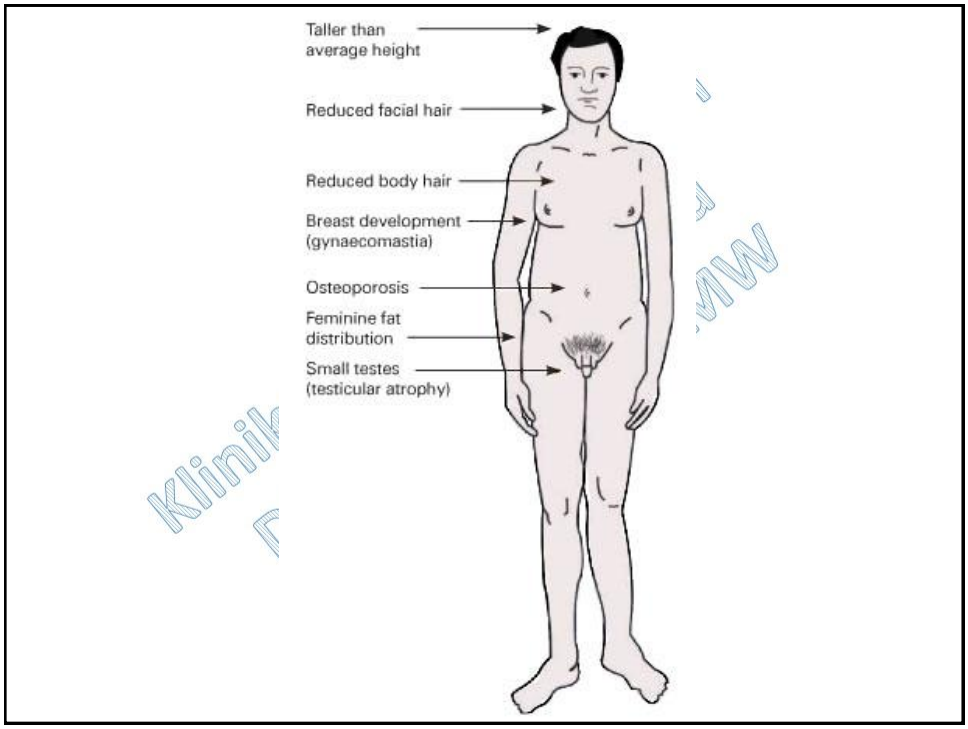
- Gonadal damage secondary to chemotherapy/radiation
- Enzyme defects in the gonads
- Androgen insensitivity
- Ovarian/testicular dysgenesis (causes of gonadal failure)

153

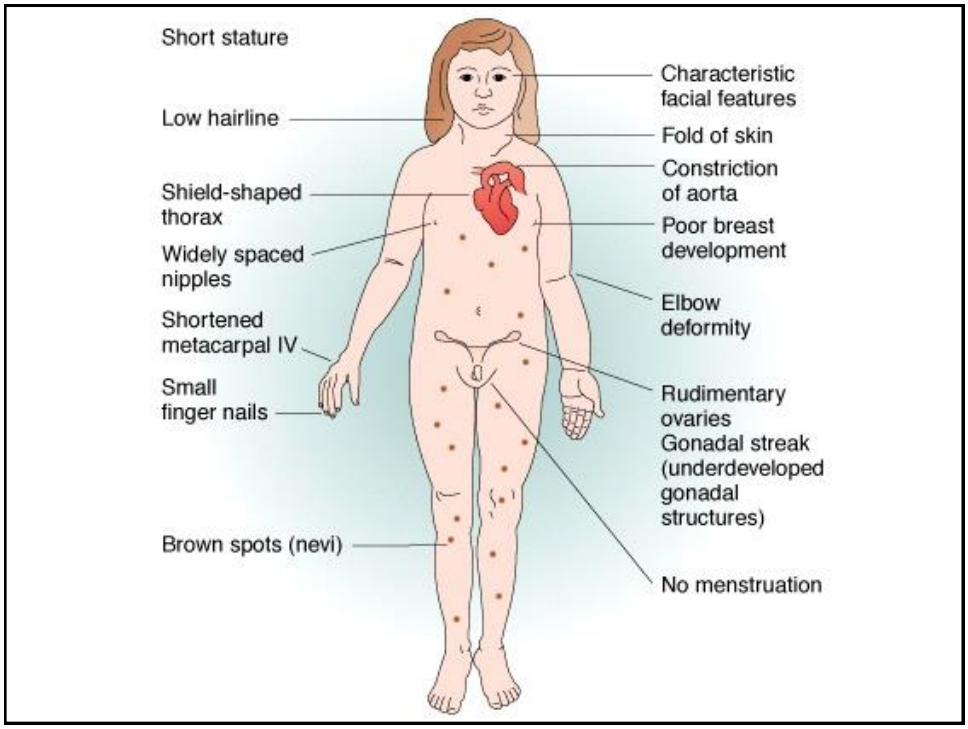
Gonadal Failure (bilateral)

- In these cases, circulating levels of LH & FSH are high (hypergonadotropic hypogonadism)
- **Congenital**
  - **Turner Syndrome**
  - **Klinefelter's Syndrome**
  - **Complete androgen insensitivity**
- Acquired
  - Chemotherapy/Radiation/Surgery
  - Postinfectious (ie. mumps orchitis, coxsackievirus infection, dengue, shigella, malaria, varicella)
  - Testicular torsion
  - Autoimmune/metabolic (autoimmune polyglandular syndromes)
  - "Vanishing Testes syndrome"
  - "Resistant Ovaries syndomre" (gonadatropin receptor problems)

154


Taller than average height
Reduced facial hair
Reduced body hair
Breast development (gynaecomastia)
Osteoporosis
Feminine fat distribution
Small testes (testicular atrophy)

155


Short stature
Low hairline
Shield-shaped thorax
Widely spaced nipples
Shortened metacarpal IV
Small finger nails
Brown spots (nevi)
Characteristic facial features
Fold of skin
Constriction of aorta
Poor breast development
Elbow deformity
Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)
No menstruation

156

Precocious puberty

Signs of pubertal maturation in:

- GIRLS < 8yrs
- BOYS <9 yrs

- Menarche < 9 yrs also indicates pubetal precocity

First signs of pubertal maturation:

- Brest budding in girls
- Increase in testicular volume in boys

157

PRECOCIOUS PUBERTY

WHAT ARE THE TYPES OF PRECOCIOUS PUBERTY?

1- Central / true precocious puberty

2-Peripheral /GnRH independent precocious puberty

3-Incomplete precocious puberty

158

CENTRAL PRECOCIOUS PUBERTY

- CPP is physiologically normal pubertal development that occur at an early age
- GnRH dependent
  ↑ GnRH pulses ⇨ ↑ gonadotropins ⇨ ↑↑ ovarian estrogen production & eventual ovulation
- It follows the pattern of pubertal changes that occur in normal puberty
- More common in girls than boys

159

CAUSES OF CPP

1-Idiopathic 80-90%

2-CNS tumors

a-Hypothalamic hamartomas

- A congenital malformation
- The most common type of CNS tumor that cause CPP
- Size & shape do not change significantly over time
- May be associated with seizures (the intrahypothalamic type)
- Rapidly progressing CPP in a child < 2 Y suggest this Dx

b-Optic glyomas
c-Craniopharyngioma
d-Dysgerminoma
e-Epindymoma
f-ganglioneuroma

160

CAUSES OF CPP

3-CNS dysfunction

a-Space occupying lesion eg. Arachnoid cyst
b-Hydrocephalus
c-Irradiation
d-Trauma
e-Infection
f-Septooptic dysplasia (congenital)
g-Excessive exposure to sex steroids
(congenital adrenal hyperplasia)

161

PERIPHERAL PRECOCIOUS PUBERTY
PPP / Pseudo PP

- **GnRH independent**
- Due to inappropriate sex hormone secretion or exposure to exogenous sex steroids
- **LH & FSH levels are low prepubertal , while estrogen ↑↑**
- May present with some or all of the physical changes of puberty

CAUSES

Exogenous sex steroids or gonadotropins

Abnormal secretion of gonadotropins (rare)
eg. Tumors secreting hCG (teratoma)

162

CAUSES OF PPP

Functioning ovarian tumors UNCOMMON

- » Granulosa cell
- » Granulosa-thica cell
- » Mixed germ cell → usually benign

} 70% present with PP

- Present with rapid progression of breast development ,
  vaginal bleeding & abdominal pain
- Palpable mass & dulling of vaginal mucosa
- Estradiol level excessively elevated
- U/S, CT, MRI, are helpful in confirming the Dx

163

CAUSES OF PPP

Functioning ovarian tumors

- – Cystadenoma
- – Gonadoblastoma

} May produce estrogen or androgen or both

- – Lipoid — Rare

Functional ovarian cysts

- – Secrete estrogen ⇨ breast development
- – Rupture or resolution ⇨↓ estrogen ⇨ vaginal bleed
- – Surgery should be avoided

Adrenal tumors RARE

Congenital adrenal hyperplasia

CHRONIC 1RY HYPOTHYROIDISM

- – TSH ⇨ acts on FSH receptors ⇨ PPP
- – Treatment ⇨ thyroxin ⇨ resolution of the PPP

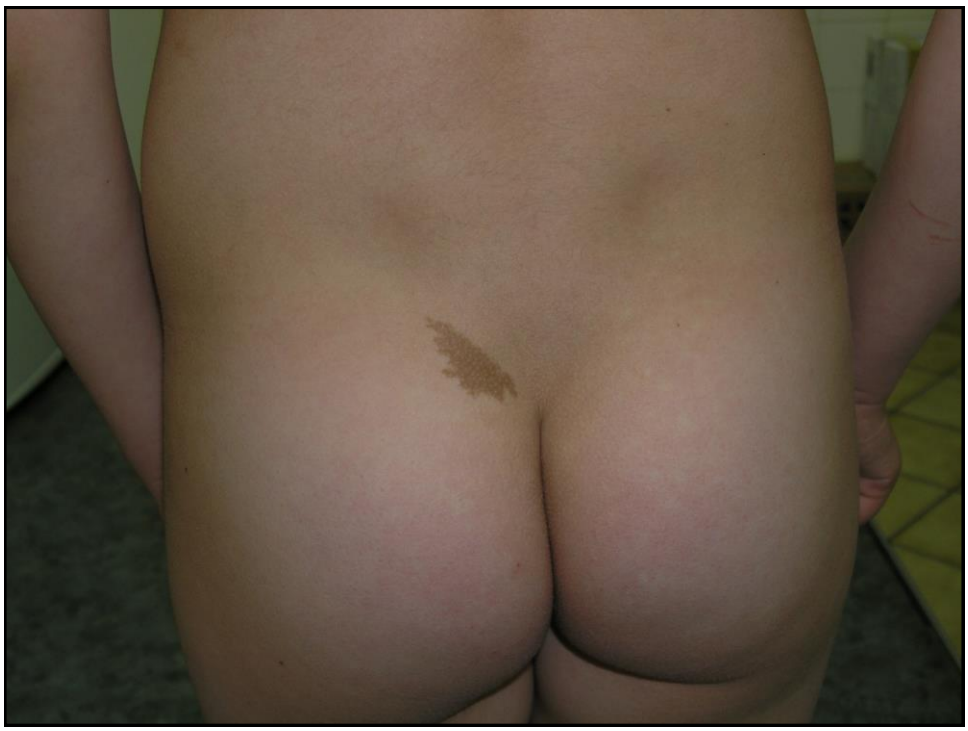
164

CAUSES OF PPP

McCune-Albright syndrome

» Café-au-lait spots
» Polyostotic fibrous dysplasia
» GnRH independent PP
» Endocrine disorder
» Autonomous functioning ovaries with 1 or 2 ovarian cysts ⇨↑ estradiol

165



168

Agenda:

1. Diabetes: diagnosis, DKA and hypoglycemia
2. Adrenals: Addisonian crisis
3. Thyroid gland: hypothyroidism, hyperthyroidism
4. Puberty: metabole & tricks
5. Growth

173

Clinical problems – too much and too little:

- Growth hormone excess: acromegaly and pituitary gigantism
- Growth hormone deficiency (GHD)

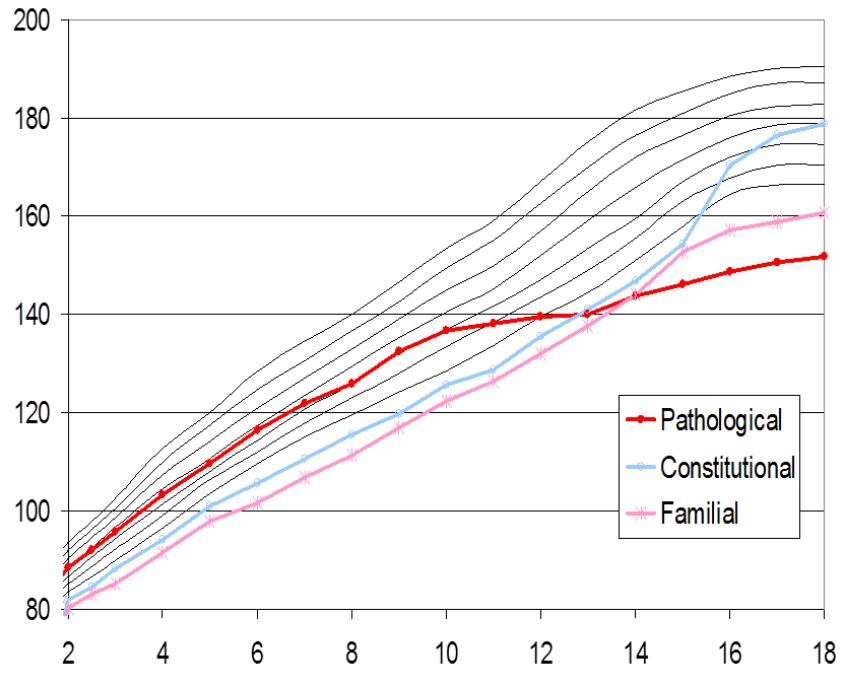
174

Approach to the patient with short stature

- **Longitudinal assessment of growth is essential child care.**
- Short stature optimally is defined relative to the genetic endowment of the individual. Short stature is recognized by comparing the individual child to a large population with a similar genetic background and, more particularly, to the mid-parental target height.
- **Growth failure (GF) is often confused with short stature**. By definition, GF is a pathologic state, whereas short stature is often a normal variant. Regardless of the genetic background, short stature may be a sign of a wide variety of pathologic conditions or inherited disorders.

  Thus, accurate longitudinal assessment of growth is a fundamental aspect of health maintenance in children. **Review of the patient's growth chart is critical to the evaluation of short stature**. Deviation from a prior growth pattern appropriate for the genetic background often heralds new pathology. In addition, analysis of the prior growth pattern helps distinguish normal from pathologic variants of short stature.

175



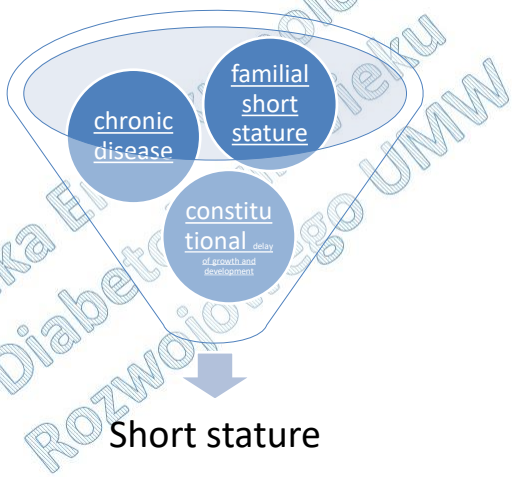
176

- Compared to a well-nourished, genetically relevant population, **short stature is defined as standing height more than 2,5 standard deviations below the mean (or below the 3 percentile) for gender**.

$$SDS = \frac{\text{Standing heigth} - \text{50 percentile}}{\text{½ (50 percentile} - \text{3 percentile)}}$$

177

The causes of short stature can be divided into 3 broad categories:



178

Endocrine diseases are rare causes of short stature.

- The hallmark of endocrine disease is linear GF occurring to a greater degree than weight loss.
- 3-5% out of 3%

179

Growth Evaluation

- **Bone age X-rays** (delayed)
- **Serum growth hormone** (low, at least 2 provocative tests are needed to diagnose GHD, in PL also night profile of GH secretion)
- **IGF-1** (low, normal ranges should be reffered to bone age and Tanner stage)
- **IGFBP-3**

180

Always think about:

- Any chronic disease that will influence growth, especially:
- Celiac disease, malnutrition
- Hypothyroidism
- Genetic syndromes (check karyotype)
- Cardiac problems (girls with Tanner syndrome)
- Cystic fibrosis

181

Most short children evaluated by clinicians in developed countries have familial short stature and/or constitutional delay of growth, **both of which are diagnoses of exclusion**.

- The hallmarks of **familial short stature** include:
  - bone age appropriate for chronologic age,
  - normal growth velocity, and
  - predicted adult height appropriate to the familial pattern.
- **Constitutional delay** is characterized by:
  - delayed bone age,
  - normal growth velocity, and
  - predicted adult height appropriate to the familial pattern.
- A first-degree or second-degree relative with constitutional delay (eg, menarche reached when older than 15 y, adult height attained in male relatives when older than 18 y).

182

Treatment:

- **GH deficiency is treated by replacing GH**.
- All GH in current use is a biosynthetic version of human GH, manufactured by recombinant DNA technology.
- As GH is a large protein molecule, it must be injected into subcutaneous tissue (or muscle) to get it into the blood.
- When the patient has had a long-standing deficiency of GH, benefits of treatment are often dramatic and gratifying and side effects of treatment are rare. Increased growth in childhood can result in dramatically improved adult height.

185

Further Care:

- **Further Outpatient Care:**
- **Monitoring the therapy:**
- **Height and weight:**
  - Track Standing height and weight and weight at 3 or 6-month intervals.
- **Lab tests:**
  - TSH, fT4
  - Glycaemia/HbA1c
  - IGF1
- **Bone age**

186

THX

192