HARRISON

EDITION 22nd

ENDOCRINOLOGY

Endocrinology

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Hypopituitarism

CAUSES

TABLE 391-1 Etiology of Hypopituitarism

- Development/structural
  - Midline cerebral defect syndromes
  - Pituitary dysplasia/aplasia
  - Primary empty sella
  - Congenital hypothalamic disorders (septo-optic dysplasia, Prader-Willi syndrome, Bardet-Biedl syndrome, Kallmann syndrome)
  - Congenital central nervous system mass, encephalocele
- Genetic
  - Combined pituitary hormone deficiencies
  - Isolated primary hormone deficiencies
- Traumatic
  - Surgical resection
  - Radiotherapy damage
  - Head injuries
- Neoplastic
  - Pituitary adenoma
  - Parasellar mass (germinoma, ependymoma, glioma)
  - Rathke's cyst
  - Craniopharyngioma
  - Hypothalamic hamartoma, gangliocytoma
  - Pituitary metastases (breast, lung, colon carcinoma)
  - Lymphoma and leukemia
  - Meningioma
- Infiltrative/inflammatory
  - Lymphocytic hypophysitis
  - Hemochromatosis
  - Sarcoidosis
  - Histiocytosis X
  - Granulomatous hypophysitis
  - Transcription factor antibodies
  - Immunotherapy
- Vascular
  - Pituitary apoplexy
  - Pregnancy-related (infarction with diabetes; postpartum necrosis)
  - Subarachnoid hemorrhage
  - Sickle cell disease
  - Arteritis
  - Snake bite venom
- Infections
  - Fungal (histoplasmosis)
  - Parasitic (toxoplasmosis)
  - Tuberculosis
  - *Pneumocystis jirovecii*
- Drug-induced
  - CTLA-4 inhibitors
  - PD-1/PD-L1 inhibitors

[a]Trophic hormone failure associated with pituitary compression or destruction usually occurs sequentially: growth hormone > follicle-stimulating hormone > luteinizing hormone > thyroid-stimulating hormone > adrenocorticotropic hormone. During childhood, growth retardation is often the presenting feature, and in adults, hypogonadism is the earliest symptom.

Abbreviations: CTLA-4, cytotoxic T lymphocyte antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.

GIRL FRIEND LIKE TO ACT

1) Developmental causes

- Pituitary dysplasia: aplasia, hypoplastic or ectopic
- Normal pituitary development: from nasopharyngeal Rathke's pouch along midline cell migration :
- Hence midline craniofacial disorders can be a/w pituitary dysplasia
- Acquired cause at birth: birth trauma, cranial haemorrhage, asphyxia and breech delivery.

Various transcription factors are involved in pituitary development

and the function of differentiated anterior pituitary cell lineages. Mutations have been described in the *HESX1, SOX2, SOX3, LHX3, LHX4, OTX, GLI2, PAX6, BMP4, ARNT2, FGF8, FGFR1, SHH, PROKR2, GPR161, IGSF1, PITX2,* and *CHD7* genes, among others. Heterozygous

All are false except

- Pit 1 : GH, PRL, TSH deficiencies MRI: Hyperplastic
- PROP1 : GH,PRL,TSH, LH, FSH(never have ACTH deficiency) , MRI: enlarged in some
- TPIT: TSH deficiency
- SF1/ NR5A1: Gonadotrophs, adrenal and Gondal development.

- Syndromic midline defects: CPHD: isolated hormone deficiency
- Based on the gen: pituitary can be hypoplastic, hyperplastic, ectopic.
- Midline defects: abnormal development of eyes, corpus callosum, vertebrae, genital systems.
- Pit 1 : GH, PRL, TSH deficiencies MRI: hypoplastic
- PROP1 : GH,PRL,TSH, LH, FSH(small minority later ACTH deficiency , MRI: enlarged in some
- TPIT: ACTH deficiency
- SF1/ NR5A1: Gonadotrophs, adrenal and Gondal development.

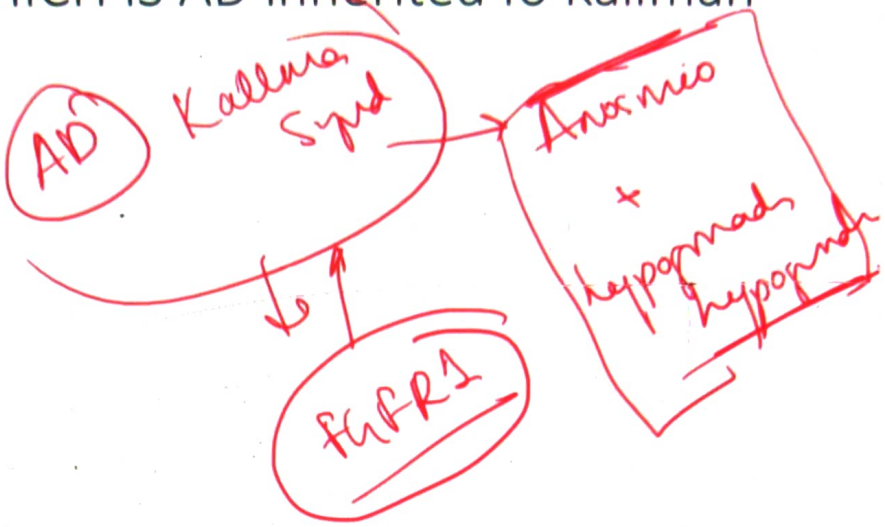
HYPOTHALAMIC ENDOCRINE DYSFUNTION

AFFECTS

- Temperature regulation
- Appetite
- Sleep wake cycles
- Autonomic systems
- Behaviour
- Memory
- Other endocrine systems

MUTATION WHICH IS AD inherited fo Kallman syndrome

- KISS1
- GPR54
- KAL 1
- FGFR1



1) Kallmann syndrome

- Defective GnRH
- a/w anosmia/ hyposmia due to olfactory bulb agenesis or hypoplasia
- a/w: colour blindness, optic atrophy, nerve deafness , cleft palate , renal abnormalities, cryptorchidism, neurologic impairments such as mirror movements
- X linked KAL 1
- AR: GPR54, KISS1
- AD: FGFR1
- OTHER: NRH1, PROK2, PROKR2, CHD7, PCSK1, FGF8, NELF, WDR11, TAC3, TACR3, and SEMA3E

C/F

- Delayed or absent pubertal development
- Low LH/FSH. With low estrogen / testosterone
- Male: HCG/ Testosterone
- Women: cyclical E+p
- FERTILITY: BY gonadotropins or [portable infusion pump

All true about bardet biedl syndrome except

- Intellectual disability
- central AVP-D
- GnRH deficiency: 75% males and 50% females will have
- Retinal degermation begins late in adulthood.

2) Bardet biedl syndrome

Retinal degeneration + BBS

- Intellectual disability
- Renal abnormalities
- Obesity
- Hexadactyly or brachydactyly or syndactyly
- central AVP-D
- GnRH deficiency: 75% males and 50% females will have
- Retinal degermation begins in early childhood and blind by 30 years
- At least 9 different loci(basal body cilia function)

3) LEPTIN/ LEPTIN RECEPTOR MUTATION

- Broad spectrum hypothalamic abnormalities (hyperphagia, obesity, hypo hypogonadism)

All false about prader willi syndrome except

- duplication of paternal copies of SNRPN gene, NECIDIN gene and other genes on chromosome 15q.
- Normal muscle tone
- Normal IQ
- Neonatal DM
- Diminished hypothalamic oxytocin and AVP producing nuclei

4) Prader willi syndrome

- Deletion of paternal copies of SNRPN gene, NECIDIN gene and other genes on chromosome 15q.
- Hyperphagic obesity
- Hypo-hypo (defective GnRH synthesis)
- Hypotonia
- Intellectual disability
- Adult onset DM
- Multiple somatic symptoms involve skull, eyes, ears, hands, feet
- Diminished hypothalamic oxytocin and AVP producing nuclei

ACQUIRED HYPOPITUITARISM

CAUSES

- TRAUMA (25-40% develop pituitary dysfunction)
- Vascular: apoplexy
- Pituitary/ hypothalamic neoplasm
- Craniopharyngioma
- Lymphoma
- Mets
- Inflammatory: hypophysistis
- Autoimmune hypophysisitis due to immune checkpoint inhibitor
- Infiltration: sarcoidosis, hemochromatosis, tb
- Radiation

1) Hypothalamic infiltration disorder

- Sarcoidosis
- Histiocytosis X
- Amyloidosis
- Hemochromatosis
- (involve both hypothalamic/ pituitary)
- Hence AVP-D is a common presentation (at least 50%)
- Other : growth retardation , hypo hypo, hyperPRL.

2) Inflammatory lesions:

- Tuberculosis
- AIDS
- Tertiary syphilils
- Granulomas and sarcoidosis

- These lesions cause extensive hypothalamic and pituitary damage.

All are true regarding radiation induced hypopituitarism except

- Mc with whole brain or head and neck irradiation
- 2/3rd: will develop hypopituitarism with median dose of 50Gy directed at skull base.
- Usually occurs 5- 15 years after RT
- Usually reflects pituitary destruction
- Pattern of hormone loss: GH deficiency is most common > LH, FSH> TSH>ACTH deficiency

3) Cranial irradiation

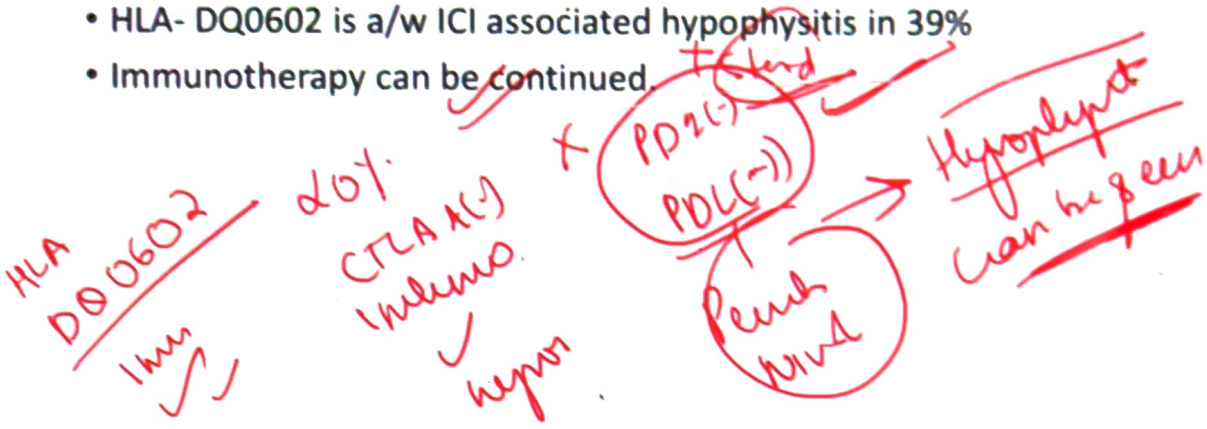
- Children , adolescents are more susceptible
- Mc with whole brain or head and neck irradiation
- It depends on irradiation dosage and time interval after RT
- 2/3rd: will develop hypopituitarism with median dose of 50Gy directed at skull base.
- Usually occurs 5- 15 years
- Usually reflects hypothalamic damage rather than pituitary destruction.
- Pattern of hormone loss: GH deficiency is most common > LH, FSH> TSH>ACTH deficiency

LYMPHOCYTIC HYPOPHYSITIS

- Mc seen in post partum women
- Usual presents with hyperprolactinemia
- MRI: prominent pituitary mass (close D/D adenoma)
- Hypopituitarism can be transient or permanent
- Rarely isolated pituitary hormone deficiencies. (selective autoimmune process)
- ESR raised
- Resolves after months of glucocorticoids

All are true about ICI hypophysitis except?

- 20% of patients receiving CTLA 4(ipilimumab) develop hypophysitis
- not seen with PD 1/ PD L1 inhibitors(pembrolizumab and nivolumab)
- HLA- DQ0602 is a/w ICI associated hypophysitis in 39%
- Immunotherapy can be continued



Immunotherapy and hypophysitits

- Pituitary cells express CTLA-4
- 20% of patients receiving CTLA 4(ipilimumab) develop hypophysitis
- Also seen with PD 1/ PD L1 inhibitors(pembrolizumab and nivolumab) may show delayed presentation
- HLA- DQ0602 is a/w ICI associated hypophysitis in 39%
- Hormone replacement with or without high dose of glucocorticoids
- Immunotherapy can be continued.

PITUITARY APOPLEXY

- Acute intrapituitary hemorrhagic vascular events
- can cause substantial damage to the pituitary and surrounding sellar structures.
- occur spontaneously in a pituitary adenoma
- postpartum (Sheehan's syndrome)
- in association with diabetes, hypertension, sickle cell anemia, or acute shock.
- Increased risk during Pregnancy
- Endocrine emergency: increased risk hypoglycemia, hypotension, shock, CNS hemorrhage , death
- CT/ MRI

- Patients with no evident visual loss or impaired consciousness can be observed and managed conservatively with high-dose glucocorticoids.

- Those with significant or progressive visual loss, cranial nerve palsy, or loss of consciousness require urgent surgical decompression.

- Visual recovery after sellar surgery is inversely correlated with the length of time after the acute event.

- Therefore, severe ophthalmoplegia or visual deficits are indications for early surgery.

EMPTY SELLA



- Mostly incidental
- a/w raised ICT
- Normal pituitary function mostly
- Small pituitary adenoma can develop from the remining rim of tissue

LABORATORY INVESTIGATION

- low levels of respective pituitary trophic hormones in the setting of low levels of target organ hormones.

TABLE 391-2 Tests of Pituitary Sufficiency

HORMONE	TEST	BLOOD SAMPLES	INTERPRETATION
GH	Insulin tolerance test: Regular insulin (0.05–0.15 U/kg IV)	–30, 0, 30, 60, 120 min for glucose and GH	Glucose <40 mg/dL; GH should be >3 μg/L
	GHRH/L-arginine test: GHRH 1 μg/kg IV and arginine 30 g IV over 30 min	0, 15, 30, 45, 60, 120 min for GH	Normal GH response is BMI dependent: 11 μg/L if BMI <25 kg/m², 8 μg/L if BMI 25-20, and 4 μg/L if BMI ≥30 Not available in the United States
	Ghrelin receptor agonist test: 0.5 mg/kg PO	0, 30, 45, 60, 90 min for GH	Normal response is GH >2.8 μg/L
	Glucagon test: 1 mg IM (1.5 mg if body weight >90 kg)	0, 30, 60, 90, 120, 150, 180, 210, 240 for GH	Normal response is GH >3.0 μg/L if BMI <25 kg/m² or if BMI 25-30 and low pretest probability, and GH >1.0 μg/L if BMI 25-30 and high pretest probability or if BMI >30
	L-Dopa test: 500 mg PO	0, 30, 60, 120 min for GH	Normal response is GH >3 μg/L
PRL	TRH test: 200–500 μg IV	0, 20, and 60 min for TSH and PRL	Normal PRL is >2 μg/L and increase >200% of baseline
ACTH	Insulin tolerance test: Regular insulin (0.05–0.15 U/kg IV)	–30, 0, 30, 60, 90 min for glucose and cortisol	Glucose <40 mg/dL Cortisol should increase by >7 μg/dL or to >20 μg/dL
	CRH test: 1 μg/kg CRH IV at 8 A.M.	0, 15, 30, 60, 90, 120 min for ACTH and cortisol	Basal ACTH increases 2- to 4-fold and peaks at 20–100 pg/mL Cortisol levels >20–25 μg/dL
	Metyrapone test: Metyrapone (30 mg/kg) at midnight	Plasma 11-deoxycortisol and cortisol at 8 A.M.; ACTH can also be measured	Plasma cortisol should be <4 g/dL to assure an adequate response Normal response is 11-deoxycortisol >7.5 μg/dL or ACTH >75 pg/mL
	Standard ACTH stimulation test: ACTH 1-24 (cosyntropin), 0.25 mg IM or IV	0, 30, 60 min for cortisol and aldosterone	Normal response is cortisol >21 μg/dL and aldosterone response >4 ng/dL above baseline
	Low-dose ACTH test: ACTH 1-24 (cosyntropin), 1 μg IV	0, 30, 60 min for cortisol	Cortisol should be >21 μg/dL
	3-day ACTH stimulation test consists of 0.25 mg ACTH 1-24 given IV over 8 h each day		Cortisol >21 μg/dL
TSH	Basal thyroid function tests: T_4, T_3, TSH	Basal measurements	Low free thyroid hormone levels in the setting of TSH levels that are not appropriately increased indicate pituitary insufficiency
	TRH test: 200–500 μg IV	0, 20, 60 min for TSH and PRL[a]	TSH should increase by >5 mU/L unless thyroid hormone levels are increased
LH, FSH	LH, FSH, testosterone, estrogen	Basal measurements	Basal LH and FSH should be increased in postmenopausal women Low testosterone levels in the setting of low LH and FSH indicate pituitary insufficiency
	GnRH test: GnRH (100 μg) IV	0, 30, 60 min for LH and FSH	In most adults, LH should increase by 10 IU/L and FSH by 2 IU/L Normal responses are variable
Multiple hormones	Combined anterior pituitary test: GHRH (1 μg/kg), CRH (1 μg/kg), GnRH (100 μg), TRH (200 μg) are given IV	–30, 0, 15, 30, 60, 90, 120 min for GH, ACTH, cortisol, LH, FSH, and TSH	Combined or individual releasing hormone responses must be elevated in the context of basal target gland hormone values and may not be uniformly diagnostic (see text)

Treatment

- Hormone replacement therapy, including glucocorticoids, thyroid hormone, sex steroids, GH, and AVP, is usually safe and free of complications.

TABLE 391-3 Hormone Replacement Therapy for Adult Hypopituitarism[a]

HORMONE DEFICIT	HORMONE REPLACEMENT
ACTH	Hydrocortisone (10–20 mg/d in divided doses)
	Cortisone acetate (15–25 mg/d in divided doses)
	Prednisone (5 mg A.M.)
TSH	L-Thyroxine (0.075–0.15 mg daily)
FSH/LH	Males
	Testosterone gel (5–10 g/d)
	Testosterone skin patch (5 mg/d)
	Testosterone enanthate (200 mg IM every 2 weeks)
	Females
	Conjugated estrogen (0.65–1.25 mg qd for 25 days)
	Progesterone (5–10 mg qd) on days 16–25
	Estradiol skin patch (0.025–0.1 mg every week), adding progesterone on days 16–25 if uterus intact
	For fertility: menopausal gonadotropins, human chorionic gonadotropins
GH	Adults: Somatotropin (0.1–1.25 mg SC qd)
	Children: Somatotropin (0.02–0.05 mg/kg per day)
AVP	Intranasal desmopressin (5–20 g twice daily)
	Oral 300–600 μg qd

All doses shown should be individualized for specific patients and should ıe reassessed during stress, surgery, or pregnancy. Male and female fertility equirements should be managed as discussed in Chaps. 403 and 404.

Vote: For abbreviations, see text.

DISORDERS OF GROWTH AND DEVELOPMENT

Growth plate consumes 10% normal energy production

- 10%
- 20%
- 30%
- 40%

Fact question

Growth plate depends on

- GH
- IGF 1
- Sex steroids
- Thyroid hormones
- FGF
- Cytokines
- Caloric energy
- AA
- Vitamins
- Trace metals
- consumes 10% normal energy production
- Hence malnutrition impairs chondrocyte growth , increases GH resiatnce lead to low levels IGF 1 and IGHFB3

Highest linear bone growth is seen during

- Infancy = 25 cm/yr
- Toddler
- Later childhood
- Puberty

1st yr

2nd : 12 cm/yr

Puh

Growth physiology

- Growth : high in infancy (pituitary dependent)
- Later childhood: 6cm/yr
- Peak growth velocity : during mid puberty : when BA: 12years(girls) and 13(boys).
- Elevated sex steroids : causes progressive epiphyseal growth plate closure
- BA: delayed in all forms of GHD or GHR defects

Clinical manifestation of GHD in children all except ?

- SS
- Micropenis
- Hyperglycaemia
- Cherubic facies

GHD in children

- IGHD
- SS, micropenis, increased fat, high pitched voice, hypoglycaemia(due to unpposed insulin)
- Familial inheritance: 1/3rd - AD/ AR/XL
- 10% have mutation in GH-N
- PROP1 and PIT1: CPHD

GHRH receptor mutation

- Severe proportionate dwarfism
- Low basal GH
- Low stimulated GH(GHRH, GHRP, ITT induced hypoglycemia)
- Pituitary hypoplasia

GH insensitivity

- GHR structure defect
- Complete/ partial GH insensitivity
- Growth failure (Laron syndrome)
- Normal or high GH with low GHBP, IGF 1
- Other causes: IGF 1, IGF 1R, IGF 1 signalling defect, STAT5B (a/w immunodeficiency)
- Rarely: GH receptor amtibody.

Nutritional SS

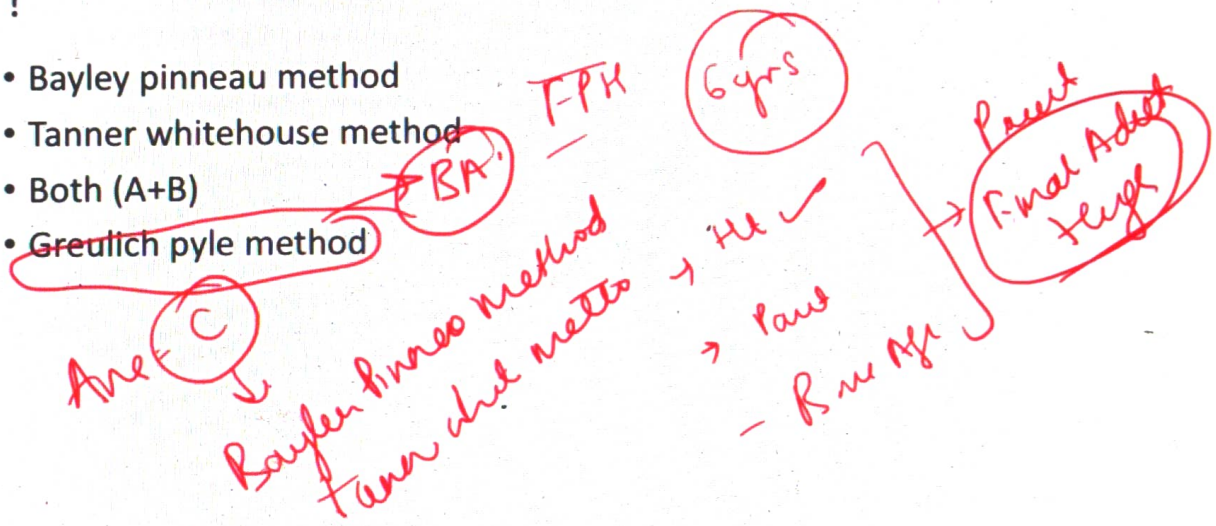
- Caloric deprivation / malnutrition
- CRF, uncontrolled DM
- All condition will have proinflammatory cytokines: which block the GH mediated signal transduction.
- Normal or high GH with low IGF 1

Psychosocial SS

- Emotional and social deprivation
- Leads to growth retardation , delayed speech, discordant hyperphagia and attenuated response to GH
- Nurturing environment restores growth rates.

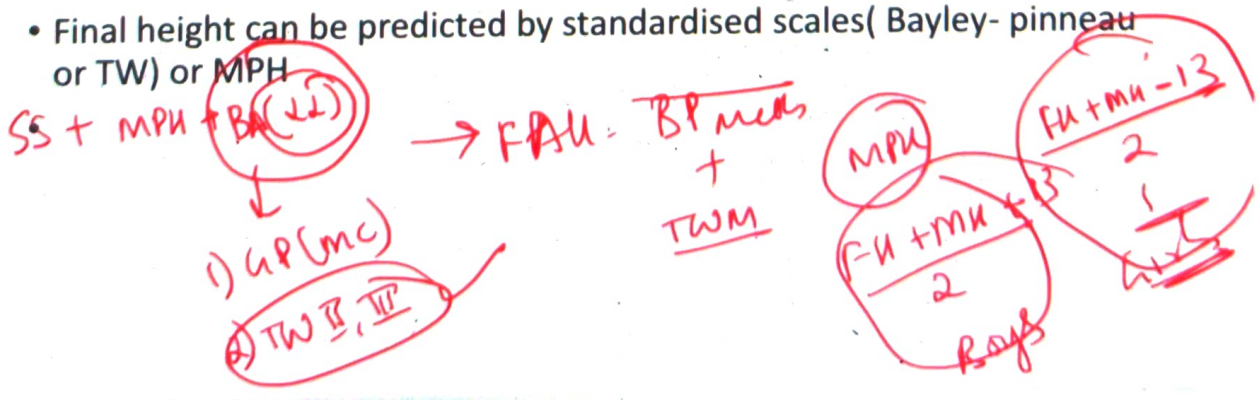
Scales used to measure final predicted height ?

- Bayley pinneau method
- Tanner whitehouse method
- Both (A+B)
- Greulich pyle method



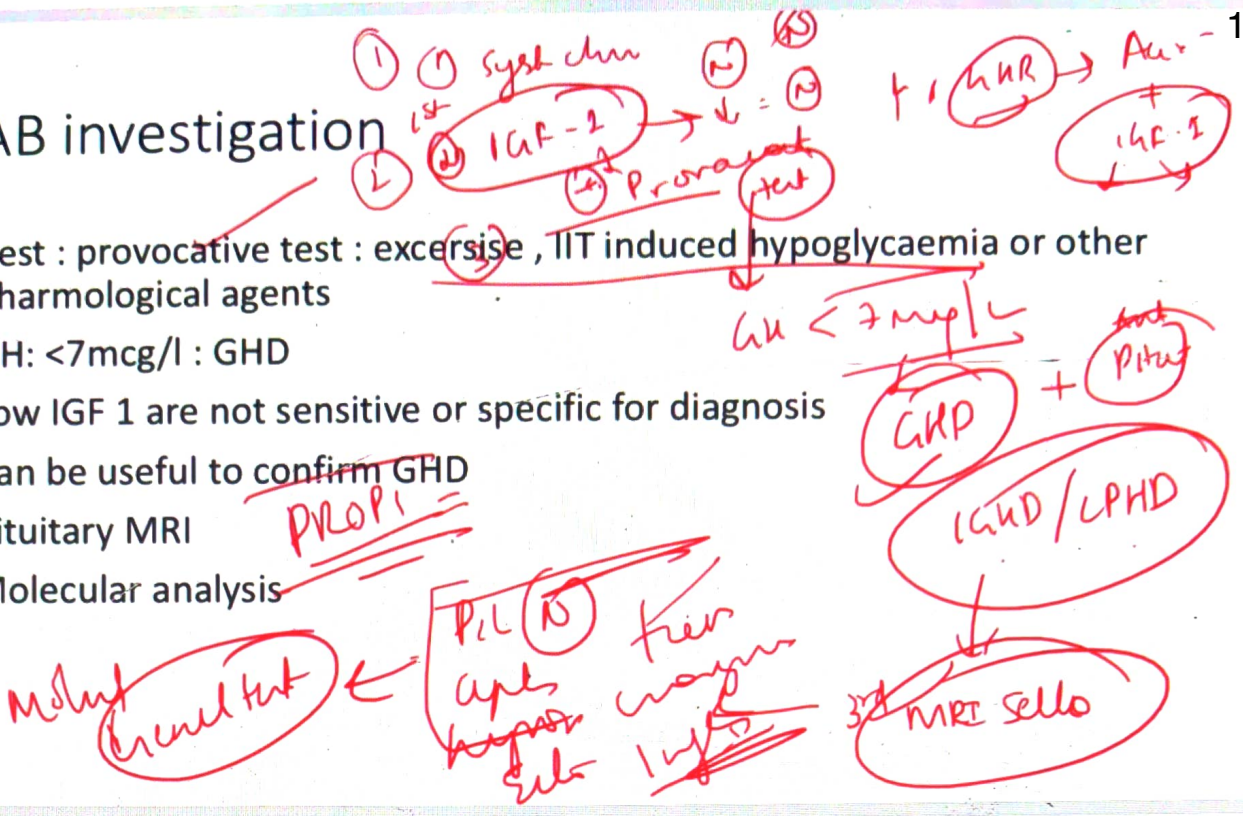
Presentation and diagnosis

- SS needs evaluation if height is < 3SD below the mean for the age or if growth rate is decelerated.
- Skeletal age can be determined by radiologic bone age(GP/ TW)
- Final height can be predicted by standardised scales(Bayley- pinneau or TW) or MPH



LAB investigation

- Best : provocative test : excersise , IIT induced hypoglycaemia or other pharmological agents
- GH: <7mcg/l : GHD
- Low IGF 1 are not sensitive or specific for diagnosis
- Can be useful to confirm GHD
- Pituitary MRI
- Molecular analysis



Treatment

- Replacement therapy with 0.02 -0.05 mg/kg/day S/C
- GV increased to 10cm/year
- Other hormonal deficiency has to be corrected
- In certain situation puberty has to be delayed with GnRH agonist/ Aromatase inhibitors

ADULT GH DEFICIENCY

Order of hormone loss in acuried hypopituitarism ?

- GH-FSH/LH-TSH-ACTH
- ACTH-GH-FSH/LH-TSH
- TSH-ACTH-GH-FSH/LH
- FSH/LH-TSH-ACTH-GH

- Mostly acquired causes
- Usually follows sequential order of hormone loss
- GH-FSH/LH-TSH-ACTH
- Patient with childhood onset GHD should be retested as adults to affirm the diagnosis .