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(Room 8)

16:30 - 17:25 WS #47: The Short and The Tall

17:35 - 18:30 WS #57: The Short and The Tall (Repeated)

Tall Stature

Size does matter!

P. Hofman

What is ‘too tall’?

Medical Definition - > 2 S.D.s above the mean

175cm Women

190cm Men

What is ‘too tall’?

A height which becomes disadvantageous, either physically or socially.

Bias of females presenting to growth clinics, but less so than in the past.

Tall stature more acceptable in males.

Disadvantages of tall stature

	Women(%) (n=73)	Men(%) (n=44)
Teasing	24.0	10.1
Clothing	29.2	28.9
Vehicles	3.1	17.4
Furniture	6.3	17.4
Others	10.4	5.8
None	26	18.8

Binder, Eur J Pediatr, 1997:905

What is normal variant tall stature?

Familial tall stature *(ie. tall parents)*

Constitutional advance in growth and development *(ie. early developers)*

Typically those presenting to growth clinics have a combination of the above and constitutes > 95% of referrals

OBESITY

Taller than peers with advanced skeletal age and pubertal maturation.

Approx. 1 S.D. taller than average.

Final height no greater than their target (or genetic) height.

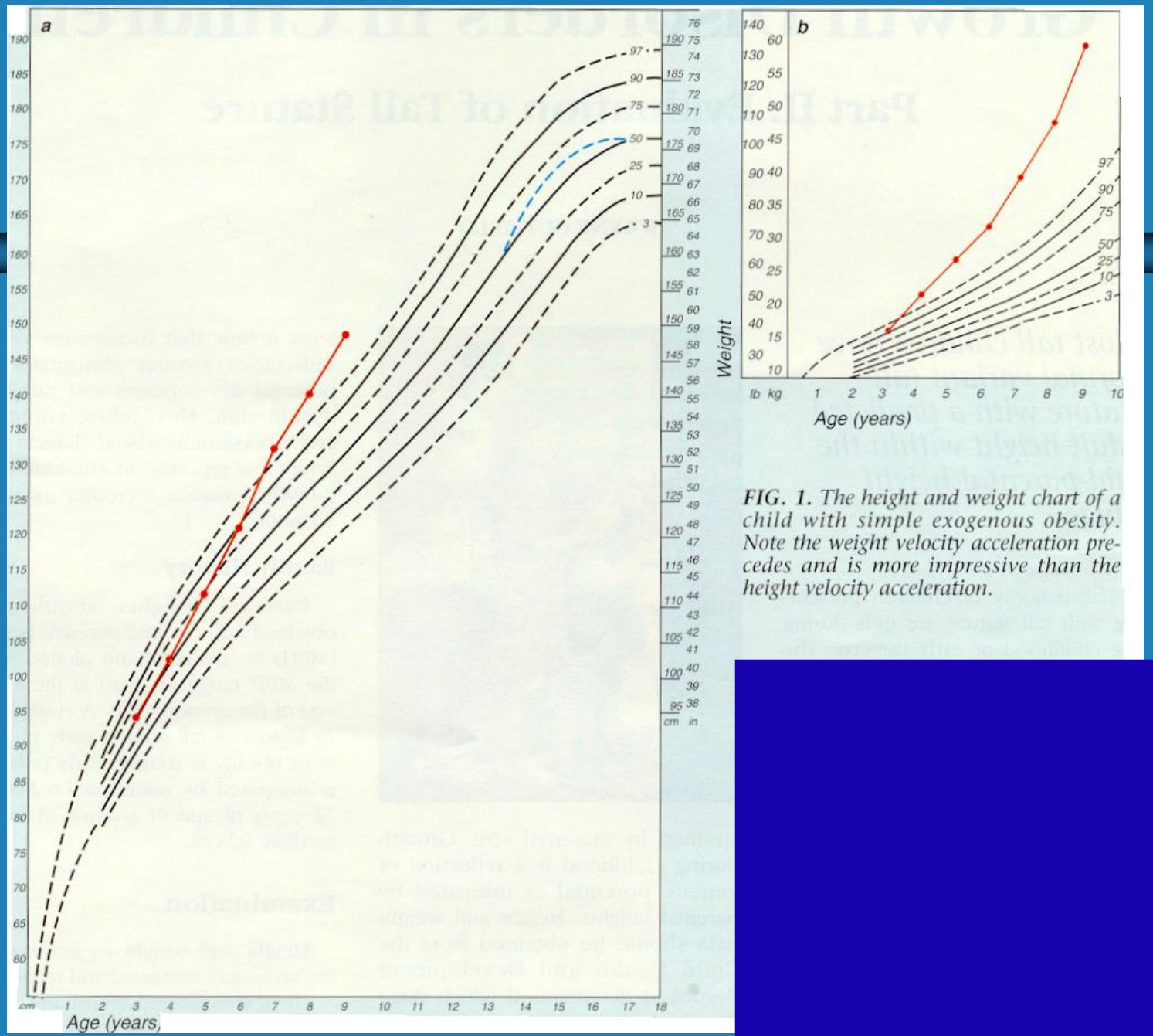


FIG. 1. The height and weight chart of a child with simple exogenous obesity. Note the weight velocity acceleration precedes and is more impressive than the height velocity acceleration.

Can tall stature indicate an underlying pathology ?

YES!

A. POSTNATAL OVERGROWTH

Nutritional - Obesity

Hormonal - Growth Hormone Excess

- 1º GH excess
- Excess GHRH secretion
- G protein mutations

- Hyperthyroidism
- Hyperinsulinism
- Prepubertal sex hormone excess
  - Adrenal or gonadal

Can tall stature indicate an underlying pathology ?

Hormonal (cont)

- Sex hormone deficiency / insensitivity
  - Eunichoidism
  - Oestrogen resistance and aromatase deficiency

Genetic

- Chromosomal
  - Trisomy X (XXX)
  - Klinefelters (XXY)
  - 47 XYY males
  - Fragile X
  - Trisomy 8

Can tall stature indicate an underlying pathology ?

Genetic (cont)

Syndromes

Marfans (fibrillin FBN 1, chrom. 15q21.1)
Beals (CCA) (fibrillin FBN 2, chrom. 5)
Homocysteinuria (cystathionine synthetase)
Neurofibromatosis

B. PRENATAL OVERGROWTH

Beckwith Weidemann Syndrome
Simpson-Golabi-Behmel Syndrome
Sotos Syndrome
Weaver Syndrome

Sex Chromosome Trisomy

47XXX

- 1:1000 female births
- Affected children are often not recognised
- IQ slightly below normal with an increased incidence of learning difficulties.
- Delay in language and speech common
- have disproportionate leg growth

Sex Chromosome Trisomy

47XXY/ 48XXYY

- 1:500 male births
- Approx. 10 cm taller than XY males
- Long legs/ firm testes
- Gynecomastia in most at puberty
- Breast Ca in 4%

Sex Chromosome Trisomy

47XYY

- 1:1000 male births
- Large teeth, nodular cystic acne
- Slight but sign. Decrease in IQ
- Increased risk of criminal behaviour
- Fertility generally normal

Prepubertal Sex Steroid Excess

Source

Adrenal	Congenital adrenal hyperplasia Adrenal tumour ACTH stimulation
Gonadal	Precocious puberty Constitutive activation of the LH receptor Constitutive activation of Gsα (MAS)

Prepubertal Sex Steroid Excess

Skeleton, especially spine, is very sensitive to sex steroid therapy after the first year of life.

Often see other signs of virilisation or feminisation

Sotos Syndrome

Features

Craniofacial -Large dolicocephalic head, prominent forehead, receding hairline, hypertelorism, down slanting eyes, prominent chin.

Pre and postnatal overgrowth

Neurodevelopmental delay (mean IQ 72)

Advanced bone age

Increased risk of tumours

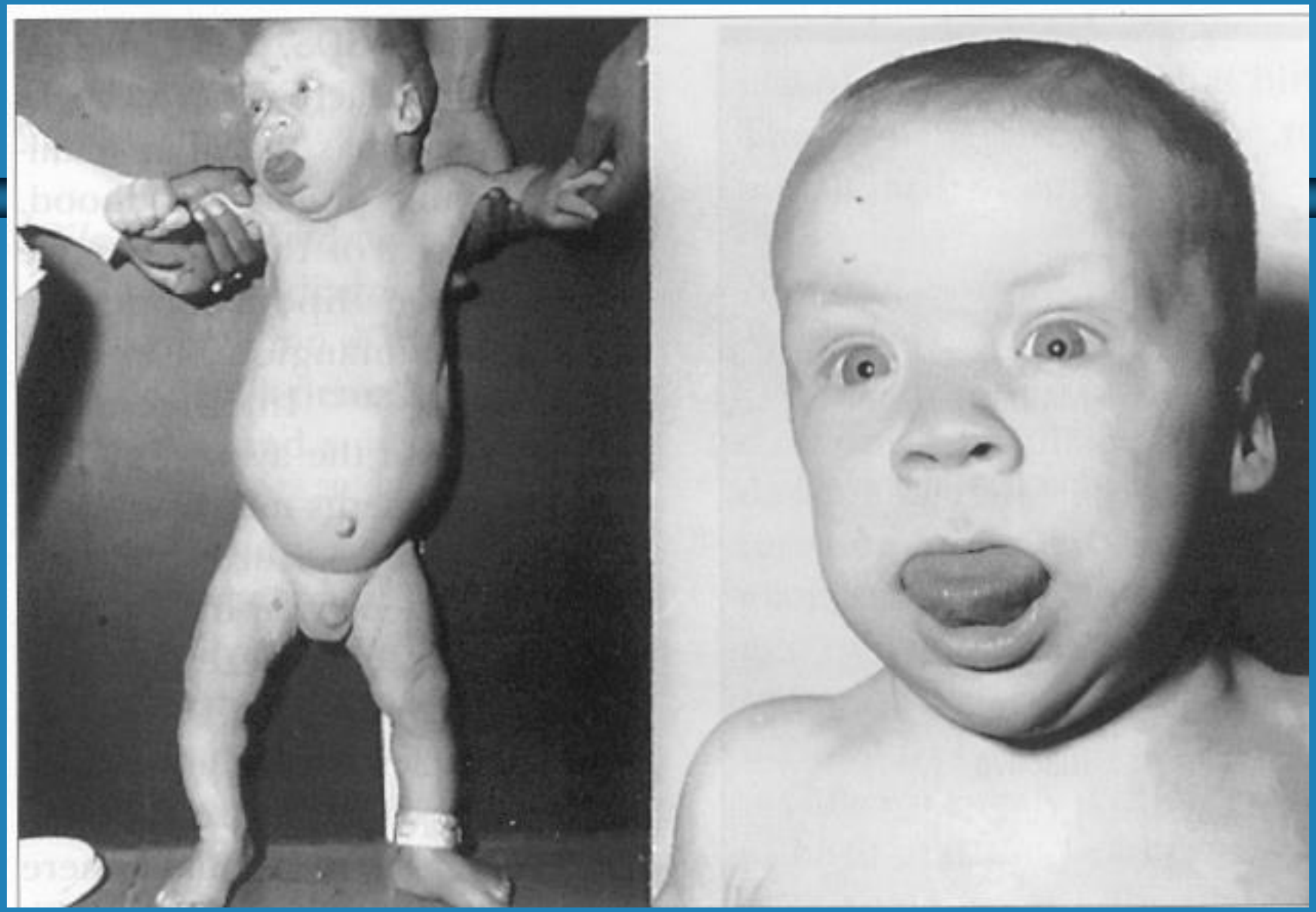
Prevalence

1:10,000-1:50,000

Beckwith-Wiedemann Syndrome

Overgrowth with advanced bone age

Craniofacial	- macroglossia, prominent eyes, capillary naevi, earlobe creases.
Malformations	- Omphalocoele, renal medullary dysplasia, hemihypertrophy (12.5%).
Other	- Hypoglycaemia (nesidioblastosis), adrenocortical cytomegaly, gonadal interstitial hypoplasia, malignant tumours (7.4%)



Beckwith-Wiedemann Syndrome

Cause is a loss of imprinting of the maternal IGF-2 gene (ie. a double dose of IGF2) on chromosome 11p15.5.

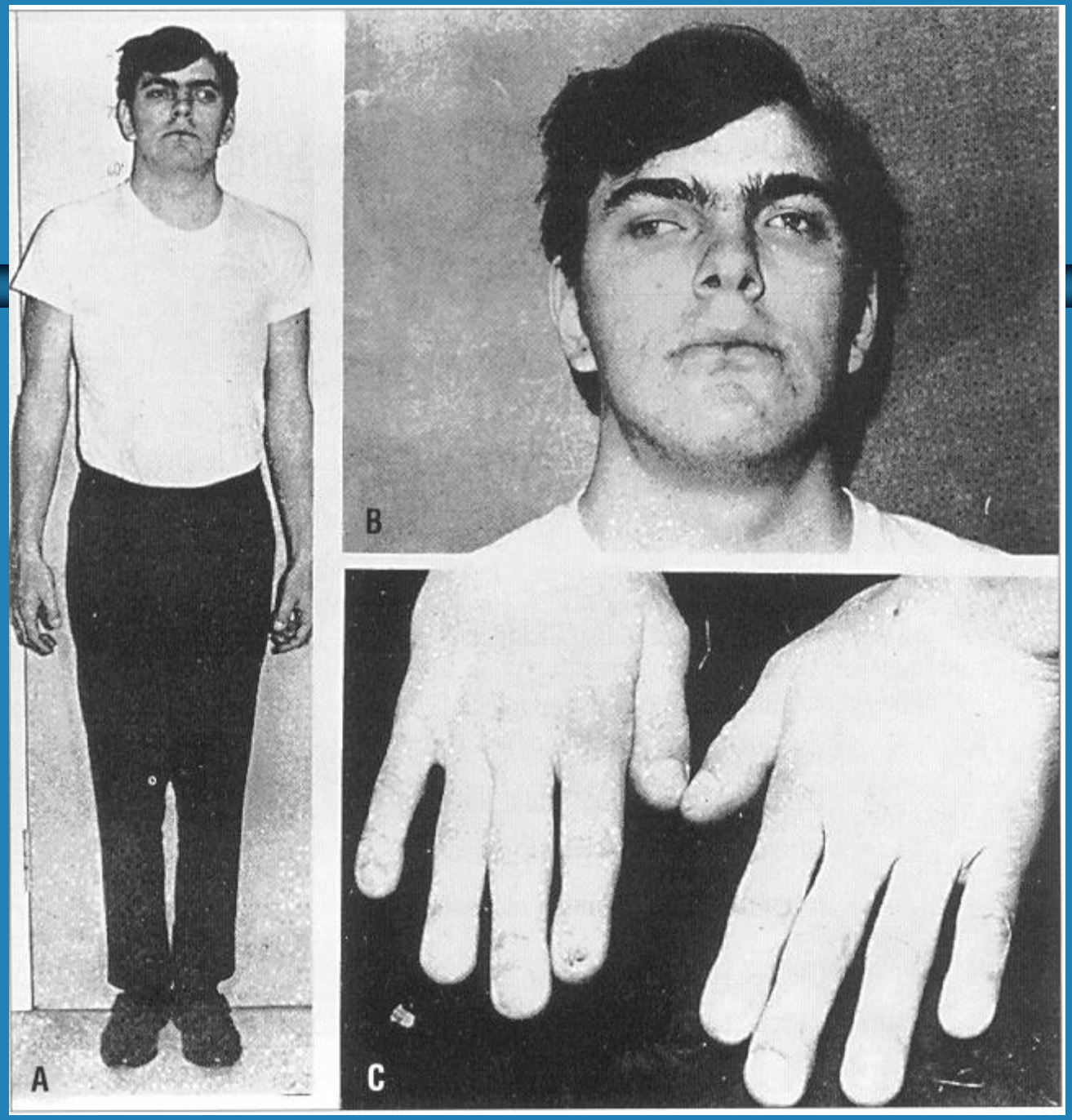
Simpson-Golabi-Behmel Syndrome

Overgrowth with advanced bone age

Craniofacial - Macrocephaly, hypertelorism, unusual facies (bulldog appearance), earlobe creases. Macroglossia, visceromegaly, hypoglycaemia (nesidioblastosis), congenital heart defect.

Other - Hypoplastic index fingernails

Inheritance - X linked recessive


A
B
C

Simpson-Golabi-Behmel Syndrome

Cause recently found to be loss of function mutations in the glypican 3 gene (Xq26).

Glypican 3 is an extracellular protein that plays an important role in growth control in embryonic mesodermal tissues.

It binds to and forms a complex with IGF2 and might modulate IGF2 action.

What are the clues to abnormal tall stature ?

Rate of growth/ growth pattern

Disproprotionate Growth (longer legs) – best assessed by measuring sitting height and/ or arm span

The patient's mid-parental or target height

(parents heights +/- 13 cm)/2

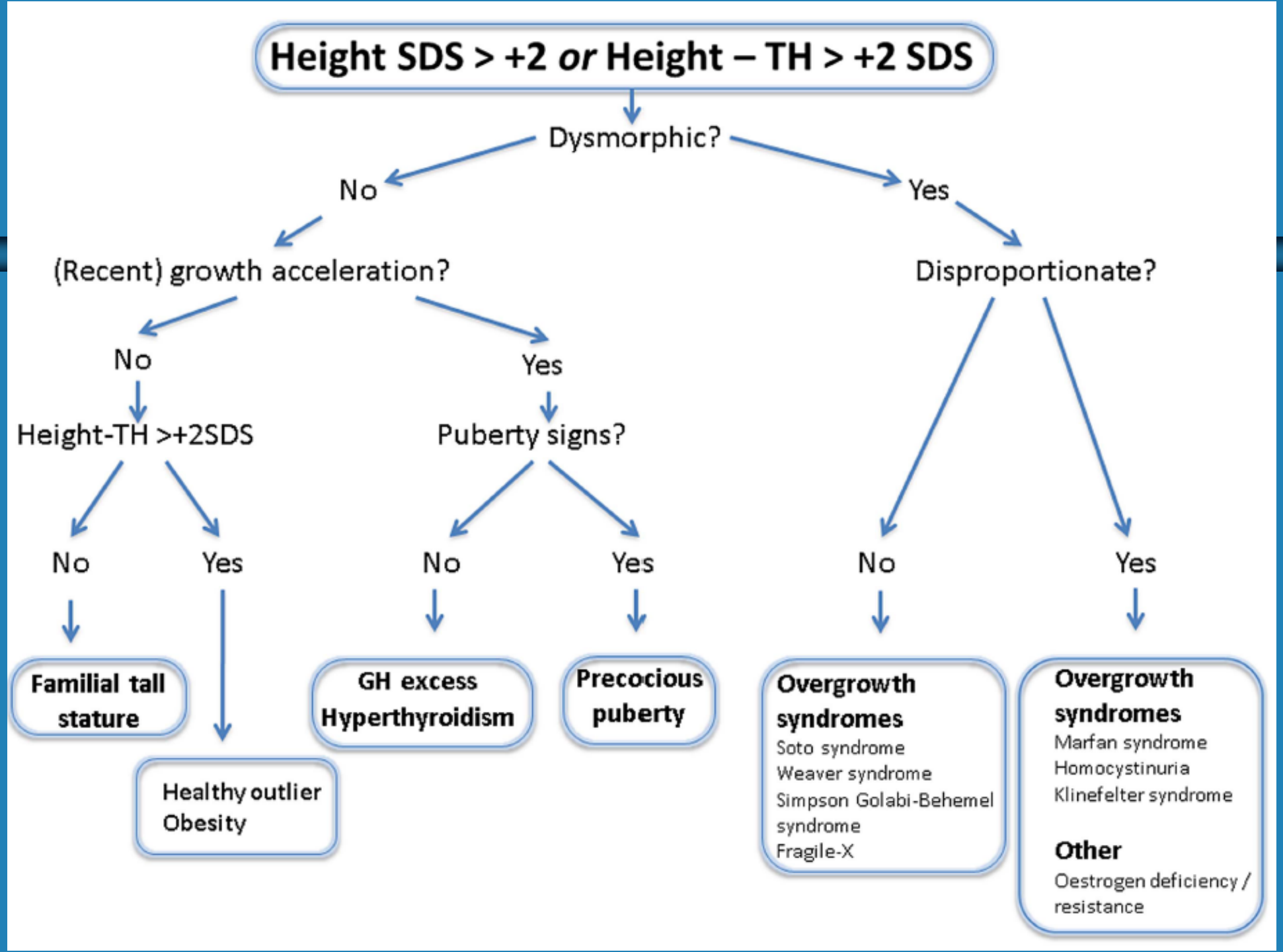
Bone age maturation/ predicted adult height

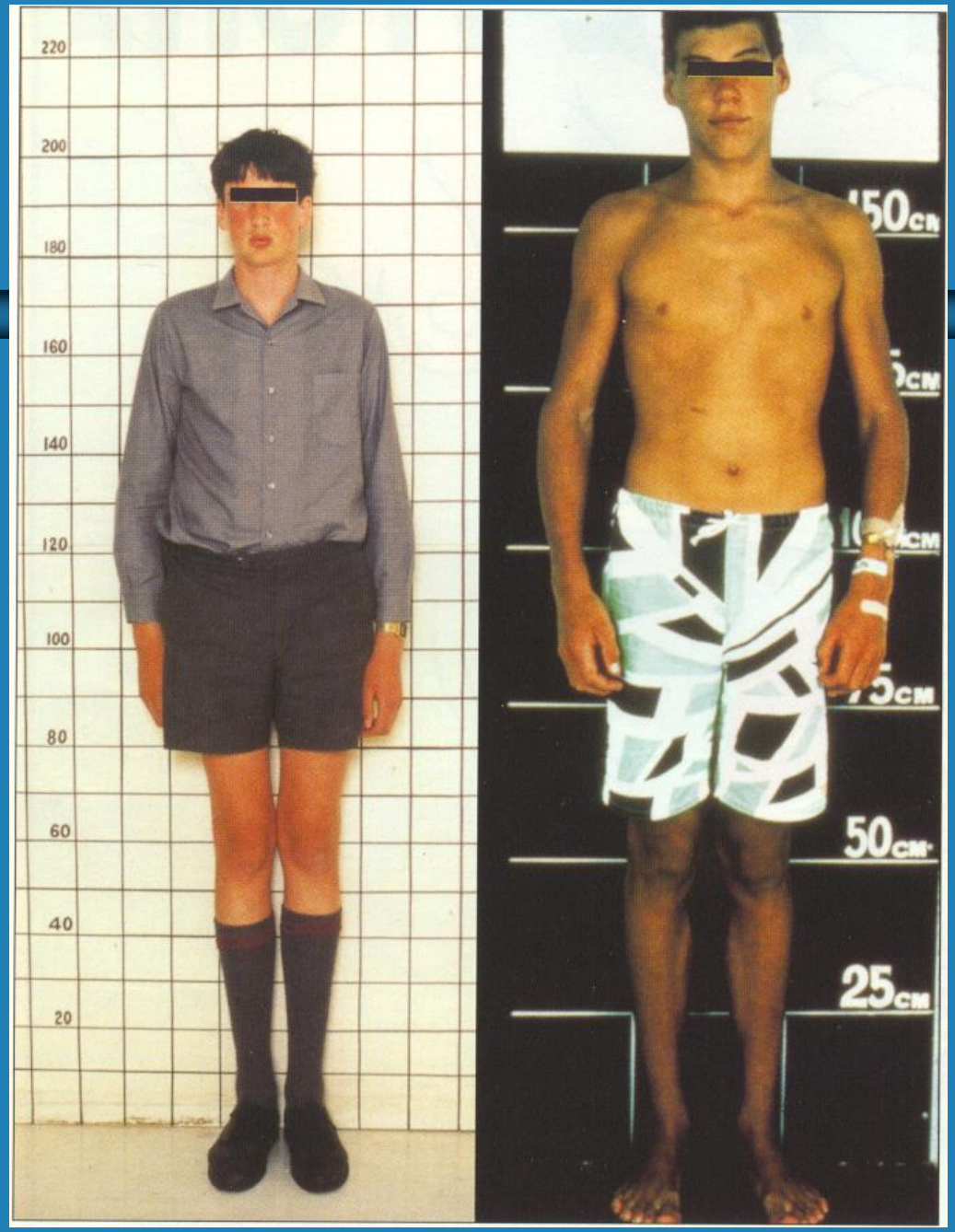
What are the clues to abnormal tall stature ?

Prenatal/ birth history

Dysmorphic features

Neurodevelopmental delay


Height SDS > +2 or Height – TH > +2 SDS
Dysmorphic?
No
Yes
(Recent) growth acceleration?
Disproportionate?
No
Yes
Height-TH >+2SDS
Puberty signs?
No
Yes
No
Yes
No
Yes
Familial tall stature
Healthy outlier
Obesity
GH excess
Hyperthyroidism
Precocious puberty
Overgrowth syndromes
Soto syndrome
Weaver syndrome
Simpson Golabi-Behemel syndrome
Fragile-X
Overgrowth syndromes
Marfan syndrome
Homocystinuria
Klinefelter syndrome
Other
Oestrogen deficiency / resistance


220
200
180
160
140
120
100
80
60
40
20
50cm
25cm

Investigations

All patients need a bone age (X-ray left hand and wrist)

Other tests depend on other findings including the result of the bone age.

Investigations

Advanced bone age

- Normal variant
- Obesity
- Sex steroid exposure
- Syndromal (Sotos, BWS, Weaver etc.)

Normal bone age

- Normal variant
- GH/ Thyroid excess
- Chromosomal
- Metabolic (homocysteinuria)
- Syndromal (Marfans, Beals, neurofib., etc.)

Investigations

Possible other tests required

TFTs
IGF-1
0800 17 OH progesterone
DHEA
androstenedione
testosterone (free)
(oestradiol)
(FSH, LH)

Management

Treatment Options

Reassure

High dose oestrogen/ testosterone tx

Combination sex steroid/ octreotide

Management

Reassurance is based primarily on a bone age derived final height prediction.

But how accurate are derived final heights?

Accuracy of final height estimation using the Bailey-Pinneau method

Author	Year	N	Pred. Ht (cm)	Actual Ht (cm)
Drayer	1997	147 girls	184.7(4.0)	184.1(4.1)
Binder	1997	79 girls	178.7(3.8)	178.5(3.6)
		52 boys	195.8(5.8)	193.9(5.1)
De Waal	1996	88 girls	181.0(3.9)	180.5(3.8)
		55 boys	198.8(5.4)	196.0(4.9)

Management

Final height prediction more accurate with increasing bone age.

The Bailey-Pinneau method tends to overestimate final height in tall children especially at younger ages (BA<11yrs).

Other methods (TW, RUS) underestimate final height.

Management

Sex steroid therapy

Goal - use supraphysiological doses of oestrogen/ testosterone to attenuate the pubertal growth spurt and fuse epiphyses.

Girls - Ethinyl Oestradiol 0.1-0.3mg PO daily

Boys - Testosterone Enanthate 500mg IM 2 weekly

Risks of treatment versus patient benefit

Risks a) Oestrogen tx (n=180)

Weight gain (>10kg)	41%
Hypertension	2%
Nausea/vomiting	14%
Vaginal discharge	13%
Menses disturbance	9%
leg cramps	20%

Most patients tolerated the side effects and did not stop therapy

de Waal, Arch dis chid,1995; 311

Risks of treatment versus patient benefit

Risks a) Oestrogen tx

The most worrying risk is thromboembolism

Incidence approx. 1:1000

May unmask a thrombotic tendency (ie antithrombin 3 protein C or S deficiency)

Be wary if patient immobilised/septic/ trauma etc.

Risks of treatment versus patient benefit

Risks b) Testosterone tx

Injection site pain/ abscess (give NSAIDs 24 hours before injection).

Severe acne

Aggression/ behaviour changes

Potential Benefits

Patient self image/ social/ practical (cars etc.)

Preexisting scoliosis

Management control of developmentally delayed child

How effective is sex steroid therapy?

Effect of Oestrogen tx on height reduction in girls

Author	Year	N	Prediction method	EE_2 (mg)	Reduction in Ht (cm)	Comments
Zachmann	1975	40	TWII	0.3	4.6	
Joss	1994	52	BP	0.1-0.5	4.2	No effect of E_2 dose on Ht
Binder	1997	56	BP	0.3	3.6	Corrected for pred. error
Weimann	1998	50	BP	0.3	5.2	

Effect of testosterone tx on height reduction in boys

Author	Year	N	Prediction method	TE mthly (mg)	Reduction in Ht (cm)
Zachmann	1975	29	TWII	1000	5.4
De Waal	1996	60	BP	1000	2.8
Binder	1997	33	BP	1000	4.4

Sex Steroid Use

Much greater reduction in height with earlier initiation of therapy.

Therapy should be continued until epiphyseal closure. In boys stopping therapy earlier can lead to an increase in final height.

Treating girls with a BA>14 yrs and boys with a BA>15 yrs does not reduce final height.

Conclusions

Most children with tall stature are normal variants.

If a child's predicted final height is outside their mid-parental height range or if there are other features suggesting pathological overgrowth they should be referred to a growth clinic.

For many tall children size does matter.