Late puberteit bij jongens
wanneer moet je behandelen?

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29-03-2023

Agenda

- Definition
- Etiology
- Clinical evaluation
- Hormonal therapy of CDGP

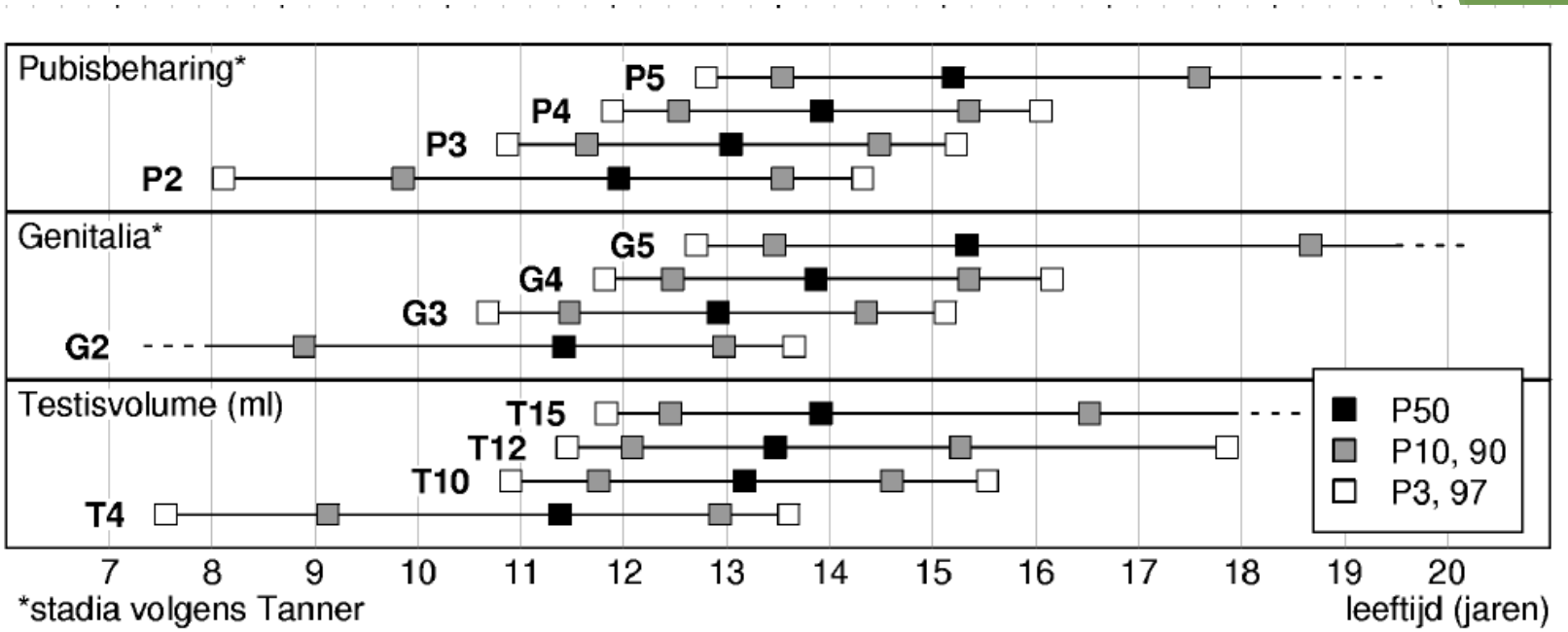
Definition

- Absence of testicular enlargment (< 4ml or <2.5cm) at an age that is 2 (2.5) SD later than the population mean

AGE LIMITS FOR PUBERTAL DEVELOPMENT (yr) (Tanner & Davies, 1985)

	PRECOCIOUS	EARLY NORMAL	MEAN	LATE NORMAL	DELAYED
centile	~99	97	50	3	~1
G_2 boys	9.0	9.5	11.5	13.5	14.0
M_2 girls	8.0	8.9	10.9	12.9	13.5
menarche	10.0	10.8	12.7	14.6	16.0

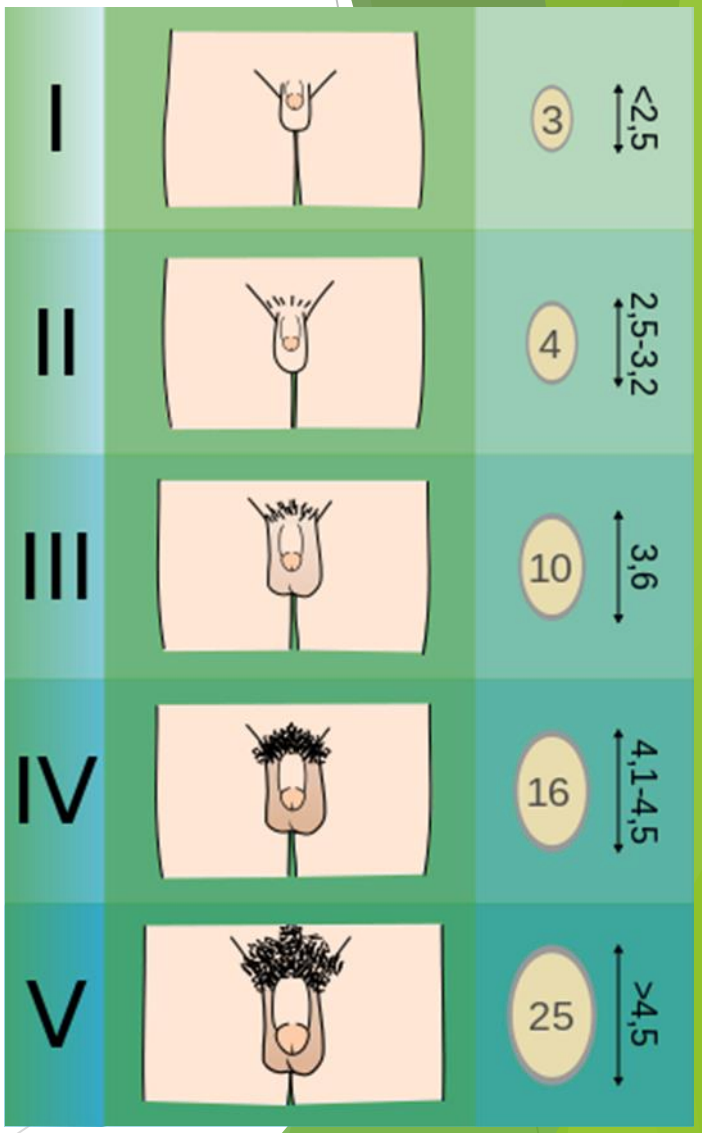
Flemish growth study 2004



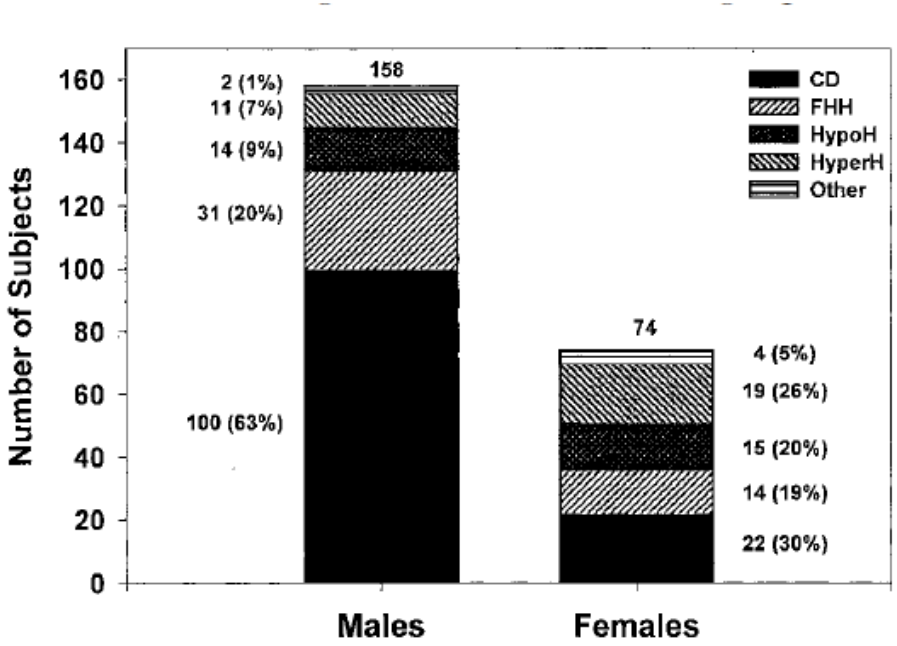
Definition

Table 2
Descriptive statistics for the timing of sexual maturity stages in males

			Time Between Stages (y)		
				Percentile	
Stage	Mean Age of Onset ±2 SD (y)	Stage	Mean	5th	95th
G2	11.6 ± 2.1	G2–3	1.1	0.4	2.2
G3	12.9 ± 2.1	PH2–3	0.5	0.1	1.0
PH2	13.4 ± 2.2[a]	G3–4	0.8	0.2	1.6
G4	13.8 ± 2.0	PH3–4	0.4	0.3	0.5
PH3	13.9 ± 2.1	G4–5	1.0	0.4	1.9
PH4	14.4 ± 2.2	PH4–5	0.7	0.2	1.5
G5	14.9 ± 2.2	G2–5	3.0	1.9	4.7
PH5	15.2 ± 2.1	PH2–5	1.6	0.8	2.7



Etiology



J Clin Endocrinol Metab, April 2002, 87(4):1613–1620

Patterns of Inheritance of Constitutional Delay of Growth and Puberty in Families of Adolescent Girls and Boys Referred to Specialist Pediatric Care

TABLE 2. Prevalence of CDGP in male and female relatives of all probands with a familial background of CDGP (at least one affected first-degree relative)

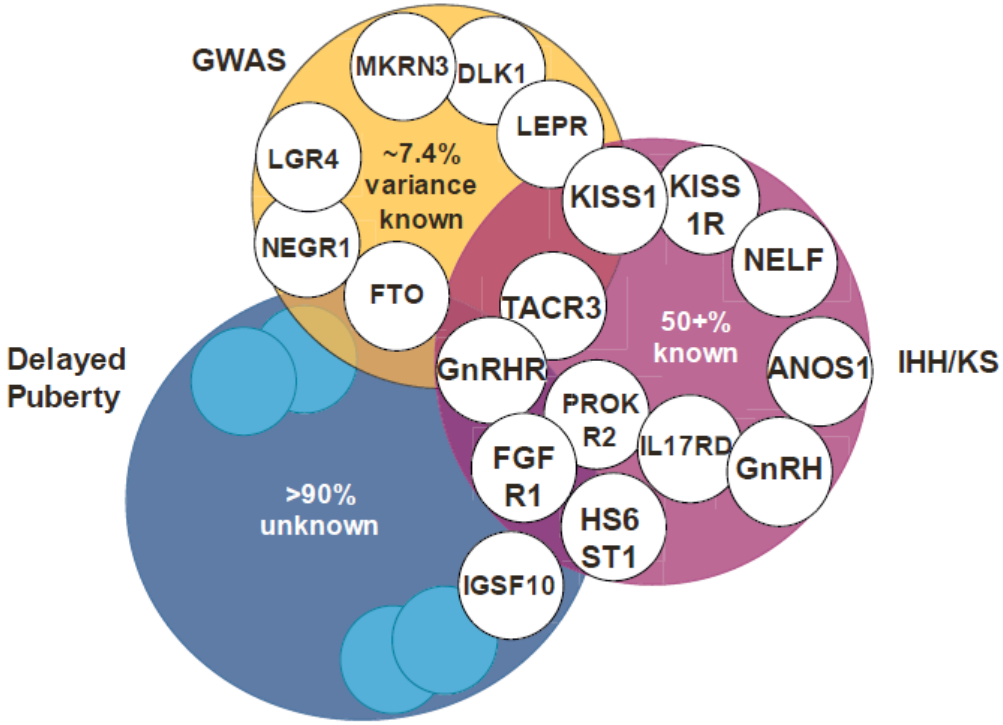
	Males	Females
First-degree relatives	79 of 148 (53%)[a]	64 of 164 (39%)[a]
All relatives	133 of 265 (50%)	128 of 290 (44%)

A Shared Genetic Basis for Self-Limited Delayed Puberty and Idiopathic Hypogonadotropic Hypogonadism

Table 3. Potentially Pathogenic Variants in Delayed Puberty Probands

Potentially Pathogenic Variant	Evidence for Pathogenicity		Identified in IHH Subject(s) (Ref.)
	Severe Variant or LOF (Ref.)	*In silico* Predictions (Deleterious Predictions/Total Predictions)*	
GNRHR p.L117R		5/5	Yes (43)
IL17RD p.K131T	LOF	3/4	Yes (16)
IL17RD p.P191 liter		4/4	No
IL17RD p.W200X	nonsense	—	No
SEMA3A p.T717I		3/5	Yes (Unpublished)
TAC3 p.H83R		5/5	No
TAC3 g.18595G>T	splice-site	—	No
TACR3 p.A171P		4/5	No

Genetic basis of delayed puberty



Neuroendocrinology
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Received: July 10, 2017
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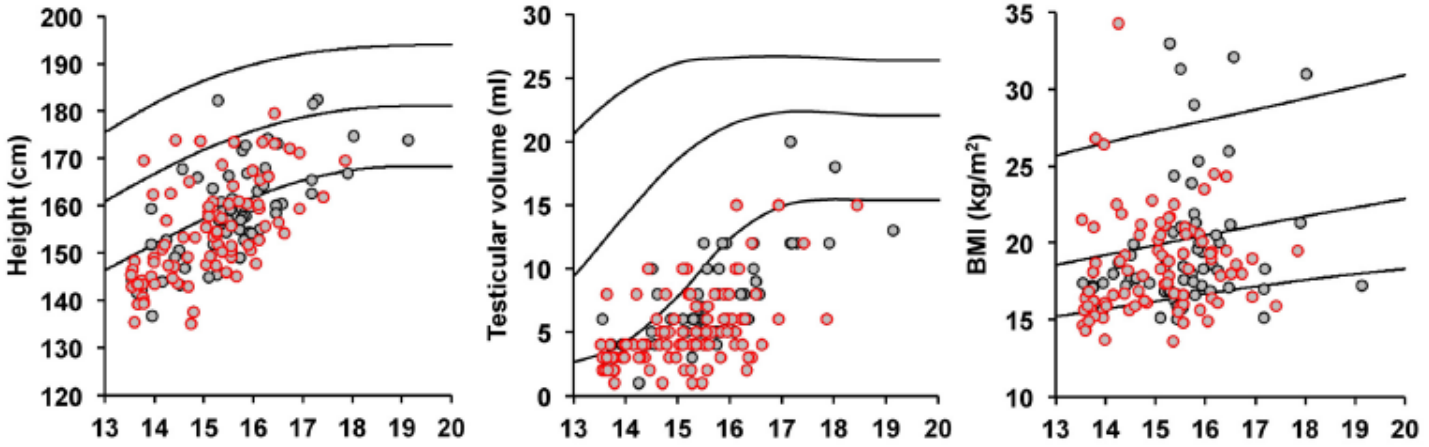
Published online: September 18, 2017

Growth and adiposity in male CDGP



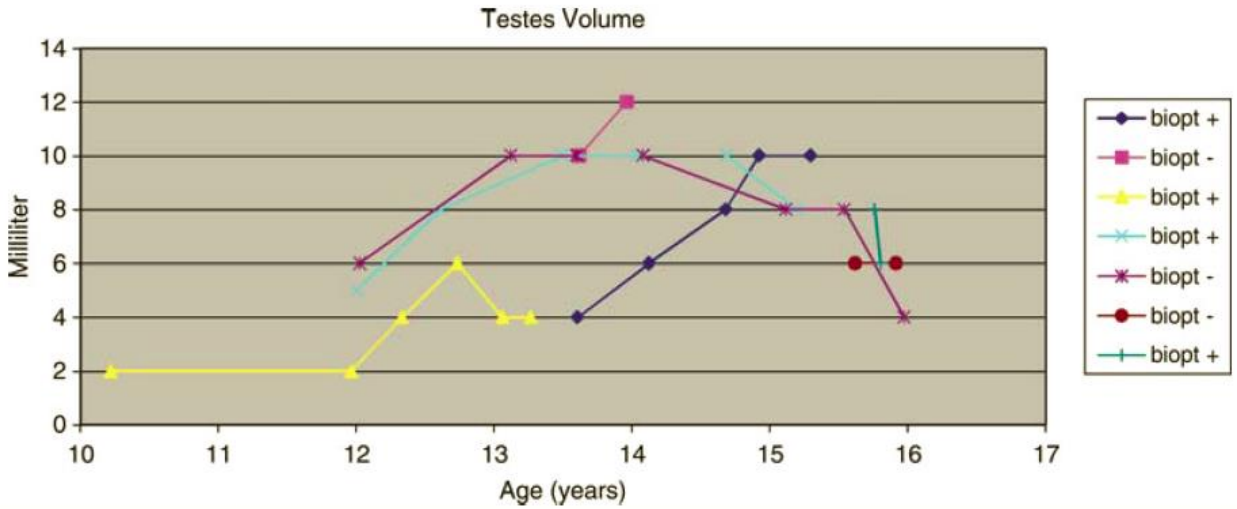
doi: 10.1210/jc.2014-3631

Etiology

Table 1. Frequency and Common Causes of Delayed Puberty Other Than Constitutional Delay of Growth and Puberty.*

Delayed Puberty	Hypergonadotropic Hypogonadism	Permanent Hypogonadotropic Hypogonadism	Functional Hypogonadotropic Hypogonadism
Frequency (%)			
Boys	5–10	10	20
Girls	25	20	20
Common causes	Turner's syndrome, gonadal dysgenesis, chemotherapy or radiation therapy	Tumors or infiltrative diseases of the central nervous system, GnRH deficiency (isolated hypogonadotropic hypogonadism, Kallmann's syndrome), combined pituitary-hormone deficiency, chemotherapy or radiation therapy	Systemic illness (inflammatory bowel disease, celiac disease, anorexia nervosa or bulimia), hypothyroidism, excessive exercise

Puberty in Klinefelter syndrome



Testes volume in adolescents with Klinefelter syndrome (KS). Biopt +, presence of spermatogonia.

Human Reproduction, Vol.27, No.4 pp. 998–1004, 2012

Etiology

Functional Hypogonadotropic Hypogonadism	Physical conditions Eg, isolated growth hormone deficiency, hypothyroidism, asthma, coeliac disease, inflammatory bowel disease, chronic renal failure, cystic fibrosis Malnutrition Eg, anorexia nervosa, poverty and starvation Overtraining Eg, athletes, gymnastics

Arch Dis Child 2016;**101**:481–488.

Evaluation

First line

- Personal and family history
- Physical signs
- Growth curve analysis
- Bone age determination
- (Eventually) biochemical & basal hormonal evaluation

to exclude or confirm (hidden) systemic disease, endocrine abnormalities, hypergonadotrope hypogonadism

Second line

- Hormonal function tests
- Brain MRI
- Genetic testing

to differentiate CDG P from permanent Hypogonadotropic Hypogonadism (HH)

Etiology

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Personal history

- Hyposmia or anosmia *
- Cryptorchidism and/or micropenis *
- Unilateral kidney *
- Dental agenesis *

- Midline facial defect (clefting, choanal atresia, coloboma)*
- Deafness *

Personal history

- Hypospadias correction *
- Chronic disease and medication use
- Delayed growth (transient in early infancy, late childhood, peripubertal)
- Delayed teeth eruption
- General & neurologic complaints *
- Abdominal pain, haematochezia *
- Weight loss & polyuria *
- Nutritional habits
- Competitive sport activities (gymnastics, long distance running)

Family history

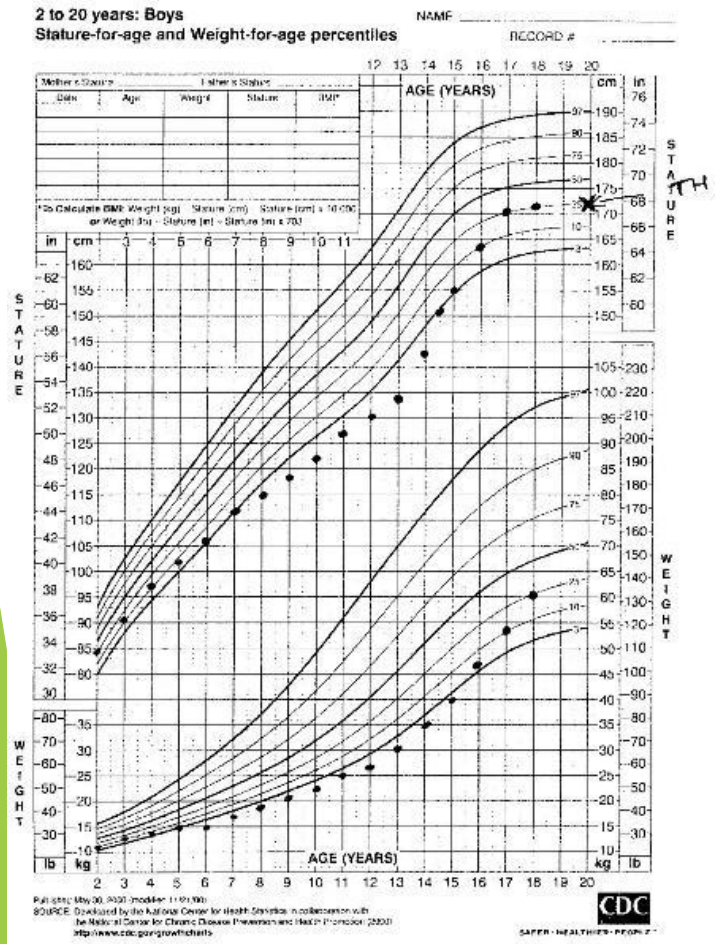
- Delayed puberty
- Sex steroid therapy
- Fertility therapy *
- Anosmia *

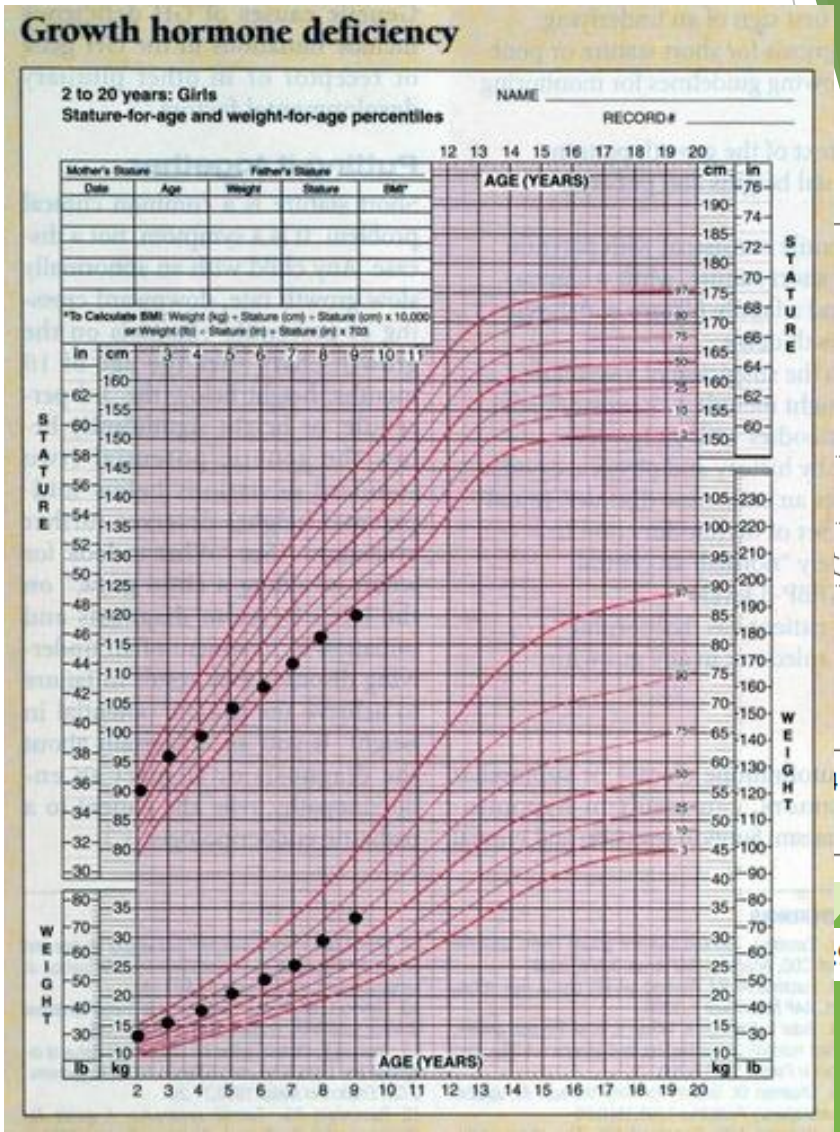
Physical signs

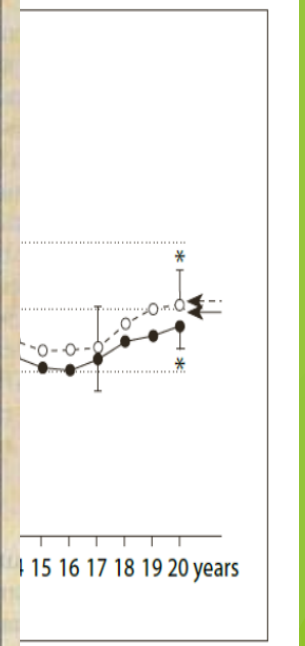
- Height, weight, BMI,Tanner staging
- Armspan, Leg length (U/L)
- Bloodpressure
- Thyroid size
- Gynecomastia
- Liver size / splenomegaly
- Testes position / size /consistency
- Penis size / hypospadias
- Visual field testing

Growth curve analysis

Constitutional Delay of Growth and Puberty(CDGP) vs GH deficiency





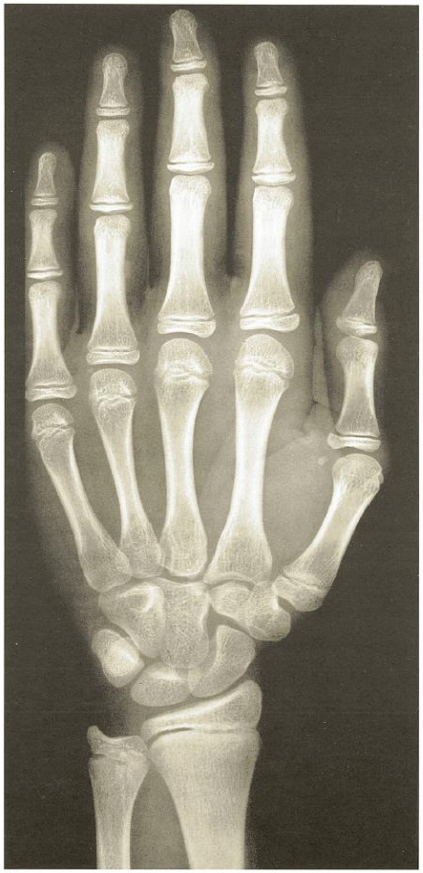


99–104

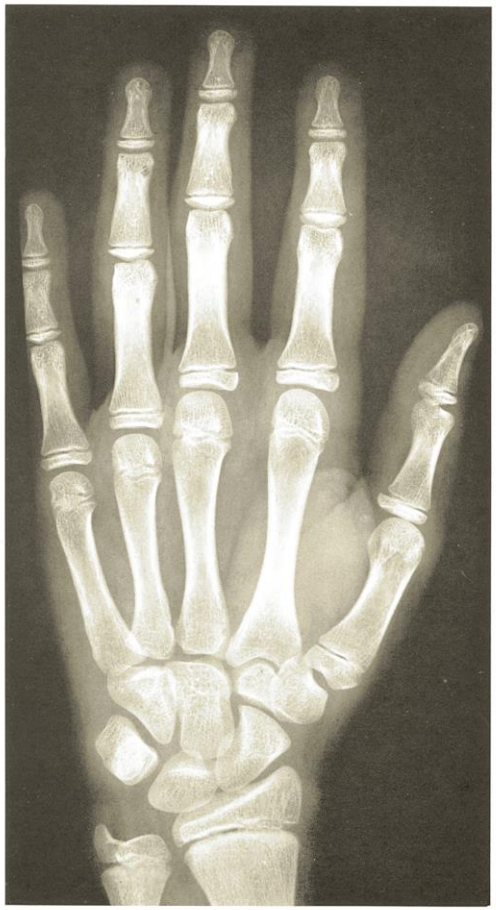
Radiological examination

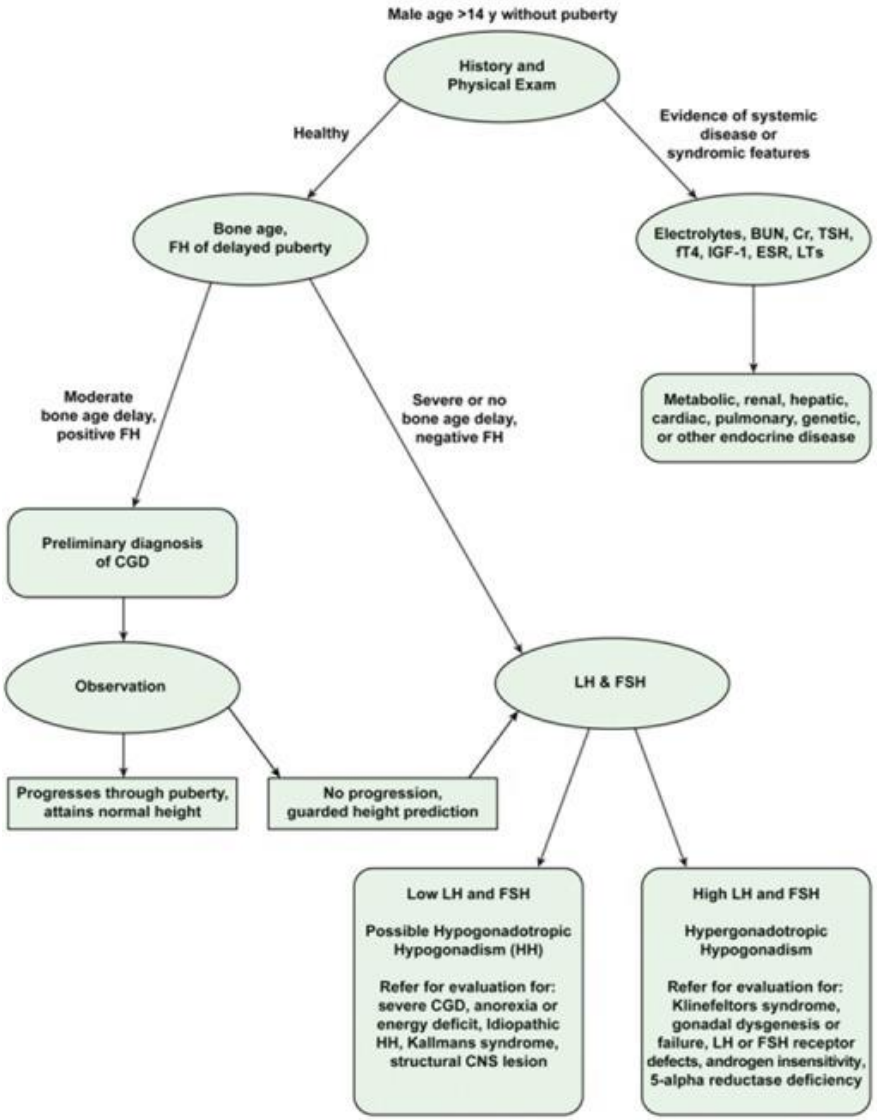
- Rx left hand and wrist

FEMALE STANDARD 19 SKELETAL AGE: 11 YEARS



MALE STANDARD 23 SKELETAL AGE: 13 YEARS





Curtis VA, Allen DB - Sports Health (2011)

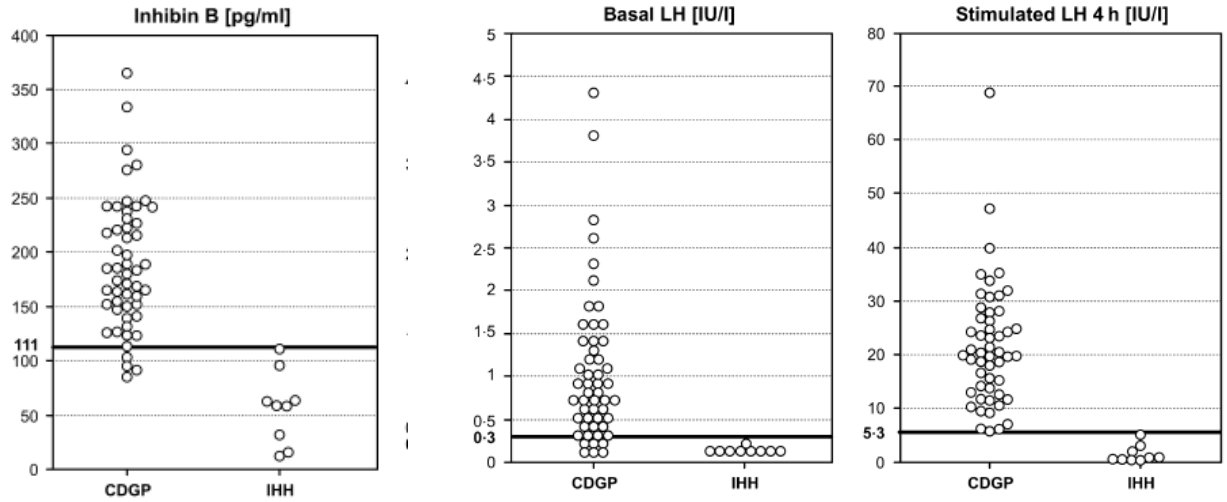
Biochemical screening & basal (before 9 AM) hormonal screening

- Sedimentation rate
- Complete blood count
- Electrolytes, Ca, PO4
- Urea nitrogen, creatinine, ALT, AP
- Anti- tissue transglutaminase antibodies
- LH, FSH, testosterone, TSH, FT4, PRL, IGF-1, DHEAS, cortisol, inhibin B

Inhibin B vs Sitmulates LH as a marker

Table 2. Comparison of the baseline clinical data of the IHH boys and the CDGP cohort (mean ± SD)

	IHH $N = 9$	CDGP $N = 52$	P
Age, years	14·6 ± 1·0	14·9 ± 0·8	0·27
Target height, SDS	0·3 ± 0·6	−0·1 ± 0·7	0·26
Height, SDS	−0·8 ± 0·7	−1·9 ± 0·9	0·001
BMI, SDS_{LMS}	0·8 ± 1·4	−0·9 ± 1·5	0·003
Bone age retardation*, years	1·4 ± 0·9	2·3 ± 0·8	0·004
Testicular volume, ml	1·6 ± 0·4	3·1 ± 0·9	<0·001



Clinical Endocrinology (2015) **82**, 100–105

Distinguishing Constitutional Delay of Growth and Puberty from Isolated Hypogonadotropic Hypogonadism: Critical Appraisal of Available Diagnostic Tests

Jennifer Harrington and Mark R. Palmert

GnRHa testing

				LH increment after stimulation: HH, 1.7–10.6 IU/liter; CDGP, 8.0–66.1 IU/liter.
10	18 males, CDGP	15.8 (15–17)	3.1 (2–4) ml	No overlap in peak LH between CDGP and HH groups, but complete overlap between prepubertal controls and HH.
11	16 prepubertal males	9.3 (6.9–11)	2.2 (2–3) ml	Peak LH results: HH, 0.1–8.6 IU/liter; CDGP, 13.5–38.1 IU/liter; prepubertal, 0.1–8.8 IU/liter.
12	13 males, CDGP	15.4 (14–21)	0.8–3 ml	No overlap in peak LH between CDGP and HH groups. Peak LH results: HH, 0.7–6.9 IU/liter; CDGP, 10.8–32.6 IU/liter.
13	19 males, CDGP	15.3 (±1.0)	4.8 (±1.8) ml	A peak LH level, <14 IU/liter had a 72% PPV and 100% NPV to identify HH. Peak LH results: HH, 3.4 ± 4.1 IU/liter; CDGP, 18.4 ± 9.4 IU/liter.
14	23 males, CDGP (1 MPHD, 3 GHD)	14.6 (12.8–17.2)	2 (2–3) ml	All patients with HH had a peak LH <5 IU/liter compared to 1 of 24 with CDGP. A peak LH level <5 IU/liter had an 89% PPV, 100% NPV for HH.
15	7 males, CDGP	14.3 (13.5–15.3)	2.6 (2–3) ml	No overlap in peak LH levels 120–180 min after leuprolide between HH and CDGP groups, but overlap between prepubertal controls and HH.
16	6 prepubertal males	9.5 (7.5–12.5)		Peak LH results: HH, 0.7–2.8 IU/liter; CDGP, 6.1–15 IU/liter.

J Clin Endocrinol Metab, September 2012, 97(9):3056–3067

Radiological examination

MRI brain (T2 coronal views of olfactory bulbs)

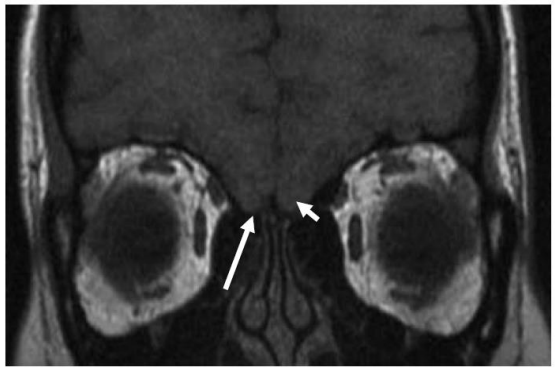


Figure 1 T1-weighted magnetic resonance imaging: bilateral olfactory bulb agenesis (long arrow) with aplastic olfactory sulci (short arrow).

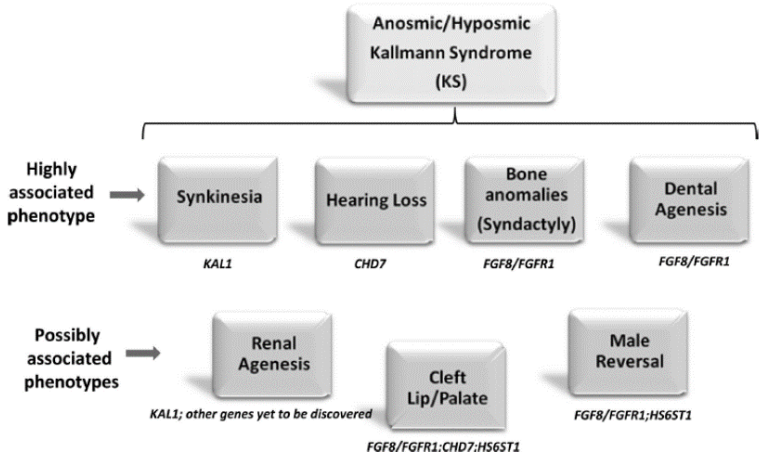
Hyposmia

Hyperprolactinemia

Other Pituitary hormone deficiency

Suspected intracranial hypertension

Genetic testing



J Clin Endocrinol Metab, May 2013, 98(5):E943–E953

Condition	Genes	
Congenital hypogonadotrophic hypogonadism (CHH)	*FSHB* *GNRH1* *GNRHR* *KISS1* *KISS1R*	*LEP* *LEPR* *LHB* *TAC3* *TAC3R*
Kallmann syndrome (KS)	*FEZF1* *HESX1* *IL17RD*	*KAL1* *SEMA3A* *SOX10*
Both CHH & KS	*AXL* ***CHD7*** ***FGF8*** *FGF17* *FGFR1**	*HS6ST1* *NSMF (NELF* *PROK2* ***PROKR2*** *WDR11*
Combined Pituitary Hormone Deficiency (CPHD)	***FGF8*** *GLI2* ***HESX1*** *LHX3* *LHX4* *OTX2*	*POU1F1 (PIT1)* ***PROKR2*** *PROP1* *SOX2* *SOX3*

Radiological examination

- DXA lumbar spine

- Family history of osteoporosis
- Suspicion of HH with or without other pituitary hormone deficiencies

Hormonal Therapy for CDGP

- IM Testosterone
- Oral Testosterone
- Dermal Testosterone

Reasons for treating CDGP with testosterone

- Limit the height deficit during adolescence
- Prevent lower muscle strength and poor sportive capacities during adolescence
- Reassure the patient by inducing genital development
- Prevent psychosocial problems (low self-esteem, depression, anxiety, social withdrawal and substance use)
- No negative effect on adult height & fertility (sometimes gynecomastia, excessive weight gain)

Final height outcome and value of height prediction in boys with constitutional delay in growth and adolescence treated with intramuscular testosterone 125 mg per month for 3 months

	Treated boys ($n = 41$)		Untreated boys ($n = 23$)		
	Mean	SD	Mean	SD	*P*-value
CA (years)	14·3	0·7	14·0	1·1	0·13
Height (cm)	144·7	6·2	144·2	6·2	0·79
Height SDS	−2·4	0·6	−2·2	0·4	0·13
BA (years)	12·0	1·2	12·3	1·3	0·36
ΔCA/ΔBA	2·3	1·1	1·7	1·1	0·02
PAH (cm)	170·0	5·0	168·1	4·1	0·15
MPH (cm)	170·4	5·5	171·1	4·5	0·59
Age at FH (years)	21·1	1·5	22·0	2·5	0·08
FH (cm)	168·9	6·0	168·2	3·5	0·65
FH SDS	−0·88	0·9	−0·99	0·5	0·62

Clinical Endocrinology (2003) **58**, 267–272

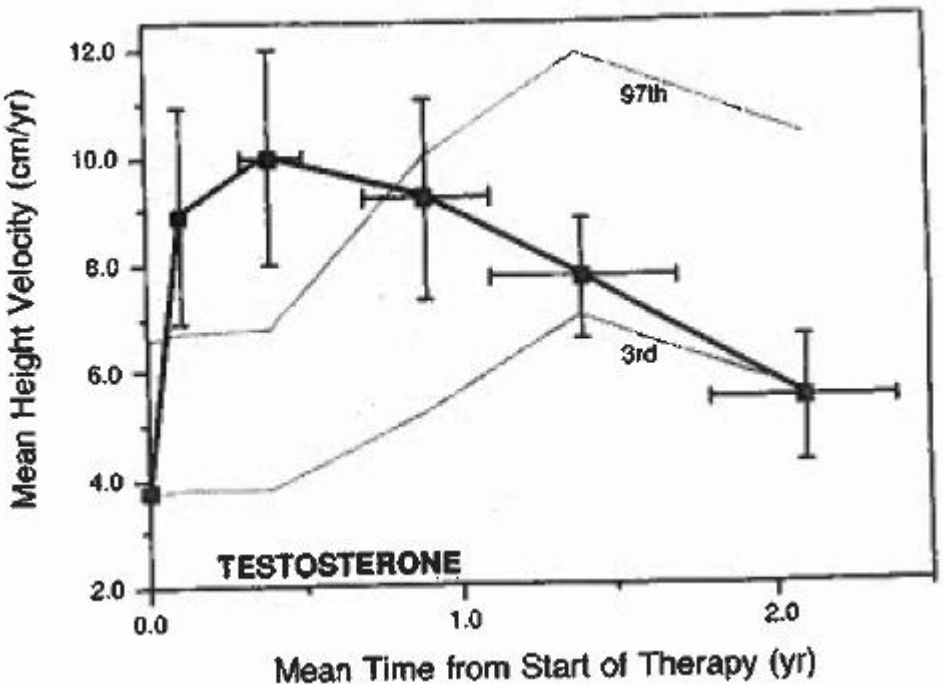


Table 1. Clinical Characteristics of 15 Boys Treated with Testosterone.*

Treatment Phase	No. of Patients†	Time from Start of Treatment	Age‡	Height‡	Weight‡	Height Velocity§	Skeletal Age‡	Height Velocity for Skeletal Age¶	Predicted Height‡	Testicular Volume‡
		yr	*yr*	*cm*	*kg*	*cm/yr*	*yr*	*percentile*	*cm*	*ml*
Pretreatment	15	—	14.1±1.0	142.2±8.6	35.0±6.3	3.8±1.3	11.3±1.5	3	170.3±7.2	5.9±2.7
Midtreatment	15	0.6±0.1	14.7±1.0	147.8±8.1	39.9±6.5	10.0±2.0	12.3±0.7	>97	172.2±6.9	7.3±2.8
End of treatment	14	1.2±0.3	15.3±1.0	153.9±8.9	44.2±6.8	9.2±1.9	13.1±0.7	90	173.5±7.4	11.3±2.7
Early post-treatment	12	1.7±0.3	15.9±1.1	158.4±9.2	48.2±7.8	7.7±1.1	13.8±0.5	8	172.9±7.1	18.0±4.7
Late post-treatment	10	2.6±0.4	16.8±1.0	163.9±9.3	53.3±7.8	5.4±1.2	14.7±0.6	3	172.2±7.8	23.2±2.7

*Plus–minus values are means ±SD. †Number of patients who completed a given treatment phase. ‡At the time of the examination.

§Calculated for the interval between successive examinations.

¶Percentile for height velocity obtained by interpolation of the data of Tanner and Davies,[8] with use of the estimated mean skeletal age at the midpoint of the interval between successive

Delayed puberty in obese boys: Comparison with constitutional delayed puberty and response to testosterone therapy

	Visit 1	Visit 2	Visit 3
Age (y)	14.9 ± 1.0	15.3 ± 1.0	15.6 ± 1.0
Height (cm)	148.9 ± 6.6	153.0 ± 6.6	156.0 ± 6.4
Weight (kg)	39.1 ± 7.6	43.3 ± 7.3	44.9 ± 7.2
BMI (kg/m^2)	17.6 ± 2.7		
Range	14.3-23.5		
Height velocity (cm/y)	4.3 ± 0.8	11.2 ± 1.6*	8.3 ± 1.5*
Weight velocity (kg/y)	2.9 ± 1.3	11.5 ± 4.2*	4.3 ± 4.0
Testis length (cm)	2.9 ± 0.4	2.9 ± 0.4	3.6 ± 0.4*
Penis length (cm)	6.5 ± 0.5	9.4 ± 1.1*	10.5 ± 1.1*
Testosterone			
nmol/L	0.8 ± 0.3	—	3.6 ± 2.6†
ng/dL	23 ± 10	—	105 ± 75
Range	10-40	—	17-229

All values are mean ± SD. Visit 1 = before testosterone treatment; visit 2 = after the last of 4 testosterone injections; visit 3 = 4 months later.
*P < .00001 versus visit 1.
†P = .00003 versus visit 1.

J Pediatr 1998;133:745-9)

	Visit 1	Visit 2	Visit 3
Age (y)	15.3 ± 1.2	15.6 ± 1.2	16.0 ± 1.2
Height (cm)	163.9 ± 6.9	167.6 ± 7.1	169.4 ± 6.9
Weight (kg)	76.1 ± 6.9	79.7 ± 4.2	83.6 ± 5.3
BMI (kg/m^2)	28.4 ± 2.4		
Range	25.1 - 31.1		
Height velocity (cm/y)	—	9.5 ± 1.6	5.2 ± 2.1
Weight velocity (kg/y)	—	9.0 ± 11.1	10.8 ± 8.3
Testis length (cm)	3.2 ± 0.5	3.2 ± 0.6	3.6 ± 0.7*
Penis length (cm)	6.6 ± 1.1	9.2 ± 1.8†	9.8 ± 2.5†
Testosterone			
nmol/L	0.8 ± 0.5	—	3.6 ± 2.1‡
ng/dL	23 ± 15	—	106 ± 61
Range	11-40	—	43-216

All values are mean ± SD. Visits 1, 2, and 3 are as defined in Table I.
*P = .024 versus visit 1.
†P < .001 versus visit 1.
‡P = .015 versus visit 1.

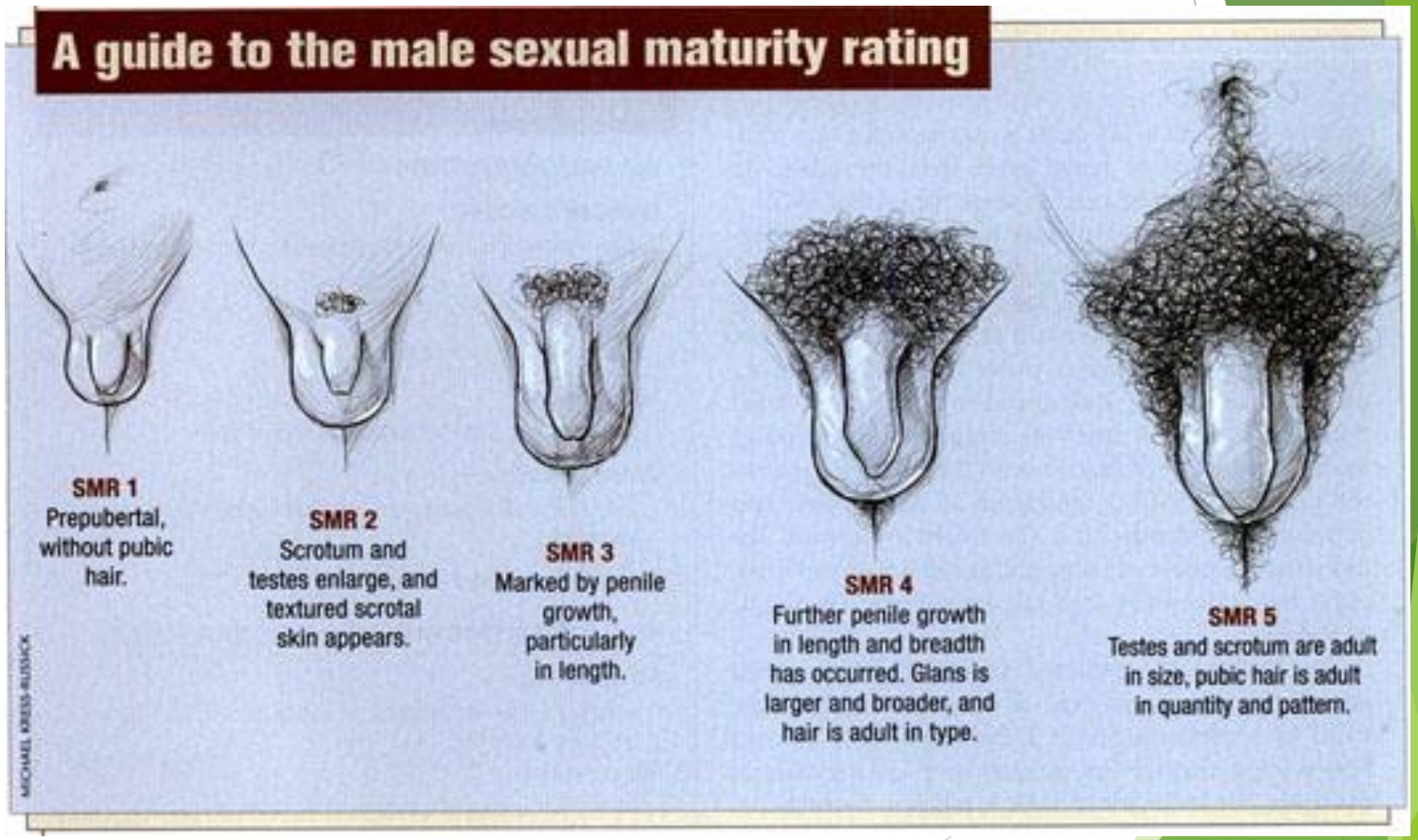
Route	Preparations	Protocol
Male		
Intramuscular	Testosterone enantate Testosterone propionate	Induction for CDGP/hypogonadism: Start at 50–100 mg every 4 weeks for 3–6 months Repeat with 25–50 mg increment (max 100 mg) Maintenance for hypogonadism: Increase gradually every 6 months to 100–150 mg/every 4 weeks Change to 250 mg 3 weekly after 3–4 years
Transdermal	Metered-dose 2% testosterone gel	Induction and maintenance for hypogonadism: Start at 10–20 mg (1–2 metered applications) daily Increase by 10 mg per 6 months to 60–80 mg in 3–4 years
Oral	Testosterone undecanoate	Induction and maintenance for hypogonadism: Start at 40 mg once daily Titrated up every 6 months to a maximum dose of 80 mg three times a day after 2–3 years

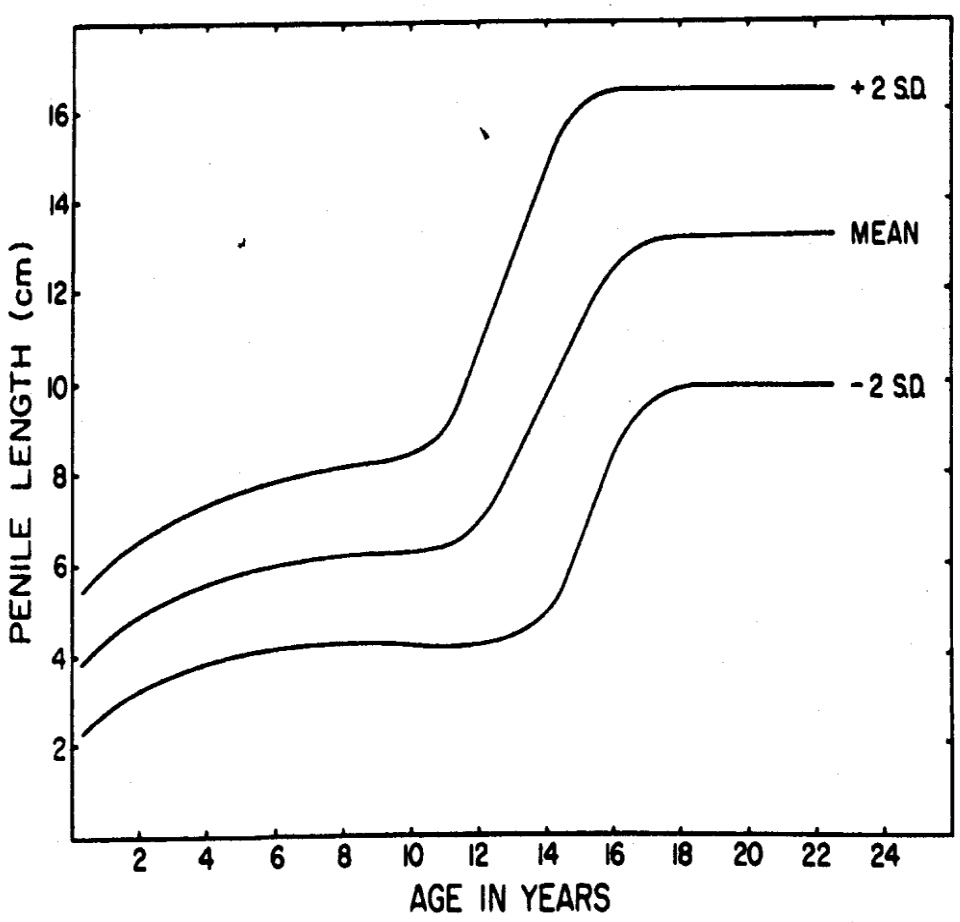
Arch Dis Child 2016;**101**:481–488.

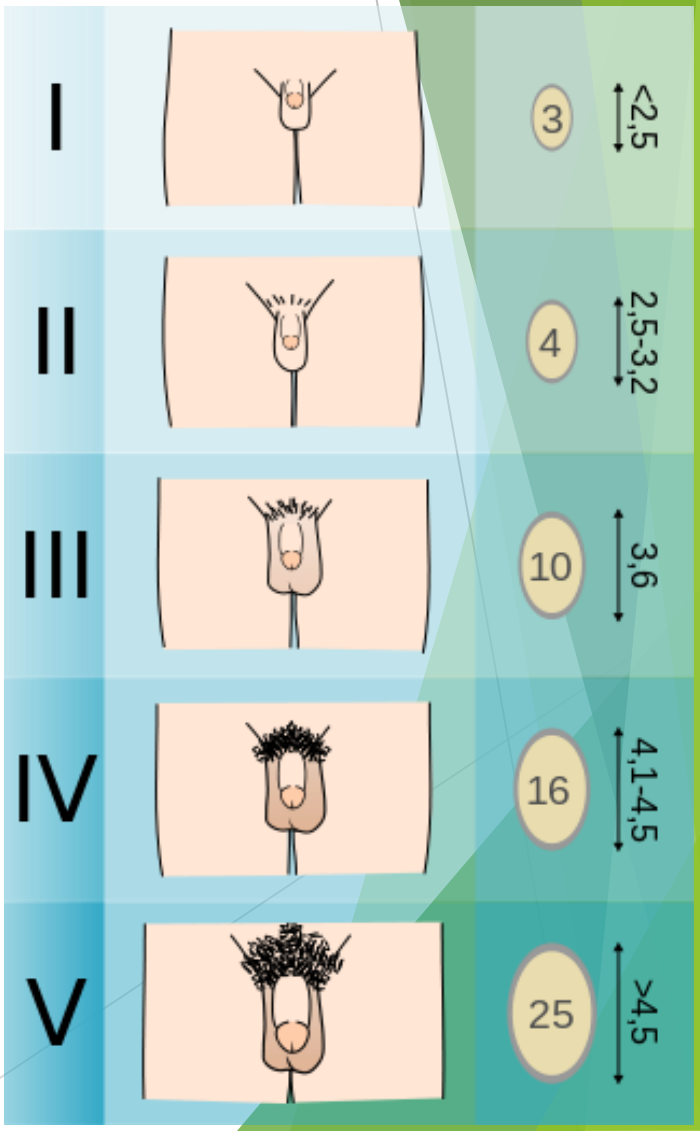
Conclusions

- No testicular enlargement at the age of 14 years needs only a more detailed biochemical & hormonal evaluation, if “ red flag “ signs are present.
- CDGP is the most frequent cause of delayed puberty, even in obese boys, but remains an exclusion diagnosis.
- Basal inhibin B is helpful in the differential diagnosis between CDGP and complete HH, but is not 100 % accurate in partial HH.
- While genital development is similar, height increase after testosterone therapy is less in obese boys.
- Genitial re-evaluation is needed 6-12 months after testosterone therapy to confirm progressive puberty.

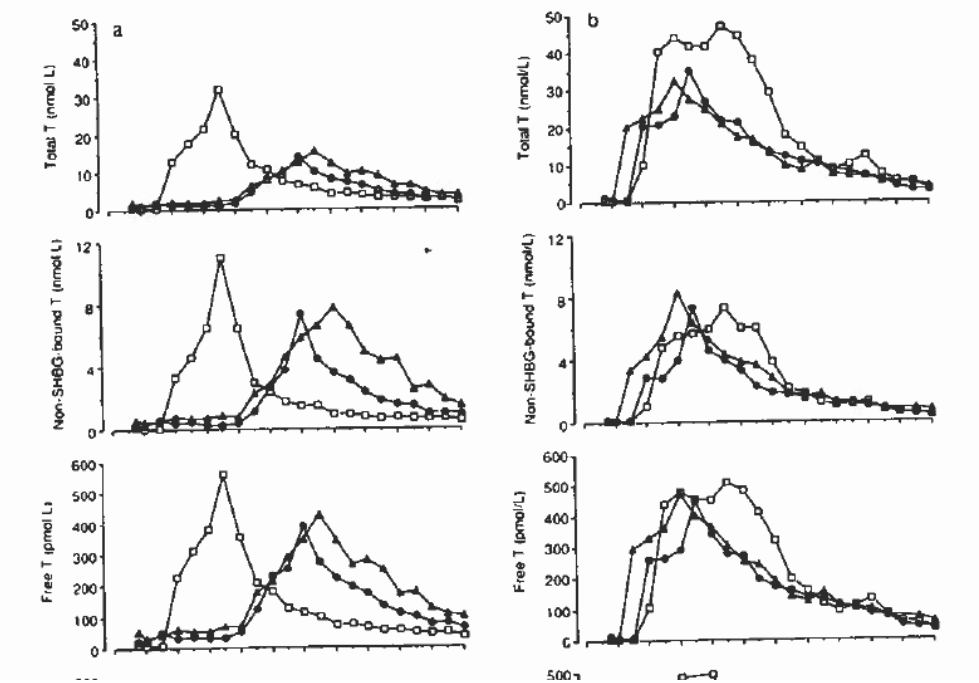
Thank you for your attention


A guide to the male sexual maturity rating
SMR 1
Prepubertal, without pubic hair.
SMR 2
Scrotum and testes enlarge, and textured scrotal skin appears.
SMR 3
Marked by penile growth, particularly in length.
SMR 4
Further penile growth in length and breadth has occurred. Glans is larger and broader, and hair is adult in type.
SMR 5
Testes and scrotum are adult in size, pubic hair is adult in quantity and pattern.
MICHAEL KRESS-RUSSICK

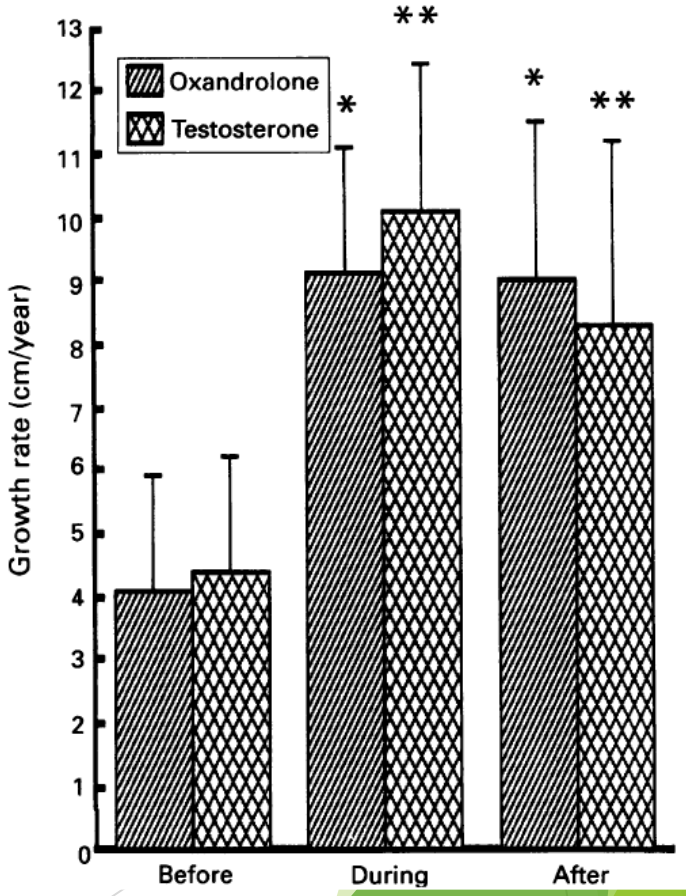

PENILE LENGTH (cm)
16
14
12
10
8
6
4
2
+2 S.D.
MEAN
-2 S.D.
2
4
6
8
10
12
14
16
18
20
22
24
AGE IN YEARS


I
3
<2,5
II
4
2,5-3,2
III
10
3,6
IV
16
4,1-4,5
V
25
>4,5

Oral treatment for constitutional delay of growth

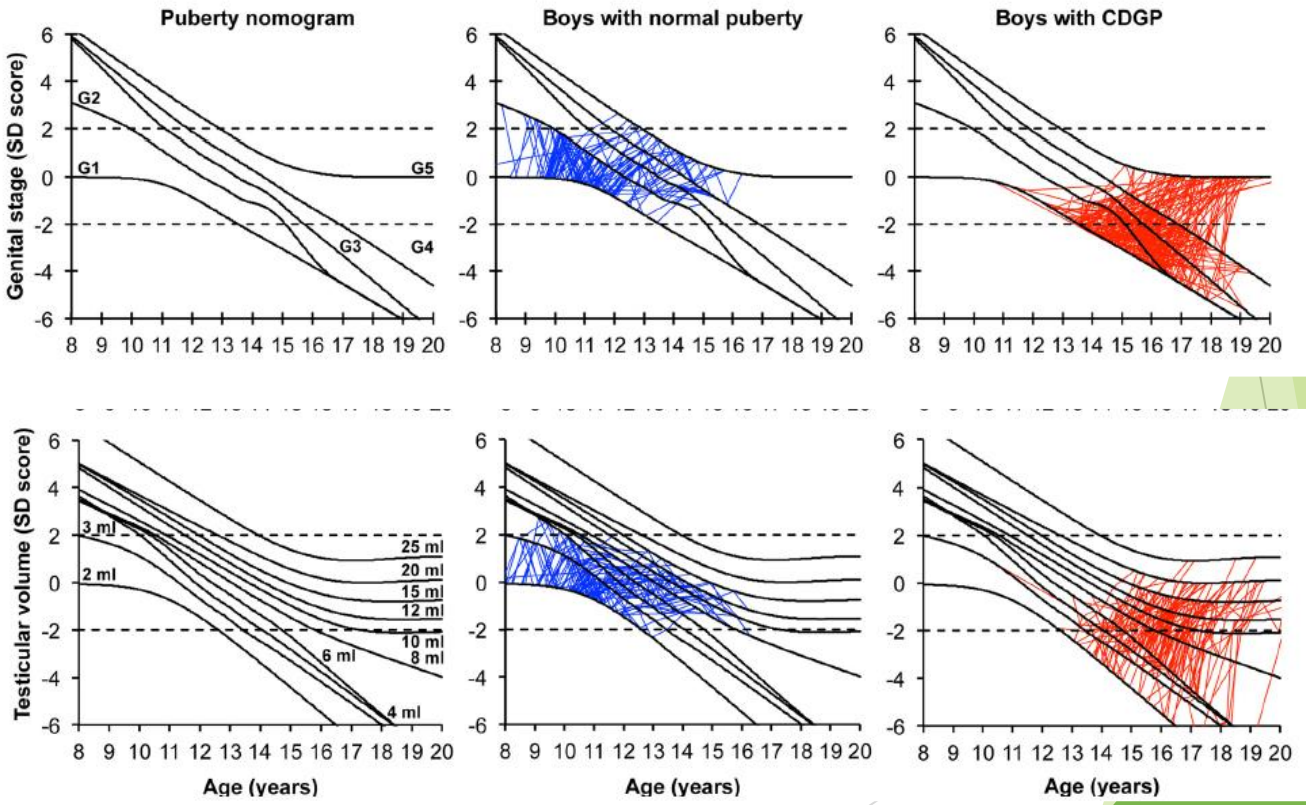


(*J Clin Endocrinol Metab* **75:** 37–44, 1992)



(*Arch Dis Child* 1994; **71:** 315–317)

Evaluation of 451 Danish Boys with Delayed Puberty: Diagnostic use of a new Puberty Nomogram and



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