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Abnormalities of Growth & Development

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OBJECTIVES

To understand the

- determinants of normal growth
- common variations in normal growth
- diagnostic approach to a child with abnormal growth
- principles of management of a child with abnormal growth

OBJECTIVES

Topics **NOT** covered in today's discussion

- Sexual differentiation
- Ambiguous genitalia and disorders of sexual differentiation
- Pubertal development
- Disorders of pubertal development – delayed / precocious
- Physiology of hormone secretion / action

Determinants of Normal Growth

Normal growth is the aggregate of hormonal, environmental, nutritional, and genetic factors

Hormonal Factors

- Thyroid – essential for normal growth
  - hypothyroidism is a common cause of severe growth delay
- Sex steroids – bone maturation is dependent on estrogen
  - testosterone can enhance GH secretion
- Glucocorticoids – potent inhibitor of growth

GH/IGF-1 Axis

Image of GH/IGF-1 Axis removed

Determinants of Normal Growth

Hormone	Growth Rate cms/yr	Adult Height
Sex Steroids ↑	Increase	Diminished
Sex Steroids ↓	Normal	Increased
Thyroxine ↑	Normal/± incr	Normal
Thyroxine ↓	Decreased	Diminished
GH ↑	Increase	Increased
GH ↓	Decrease	Diminished
Cortisol ↑	Decrease	Diminished
Cortisol ↓	Normal	Normal

Normal Growth

Anthropometric parameters

- Weight
- Measurement of height – Stadiometer

  less than 2yrs of age – length (supine)

  greater than 2 yrs of age – height (erect)
- Head circumference
- Span
- Upper segment / lower segment ratio

Normal Growth

Anthropometric parameters

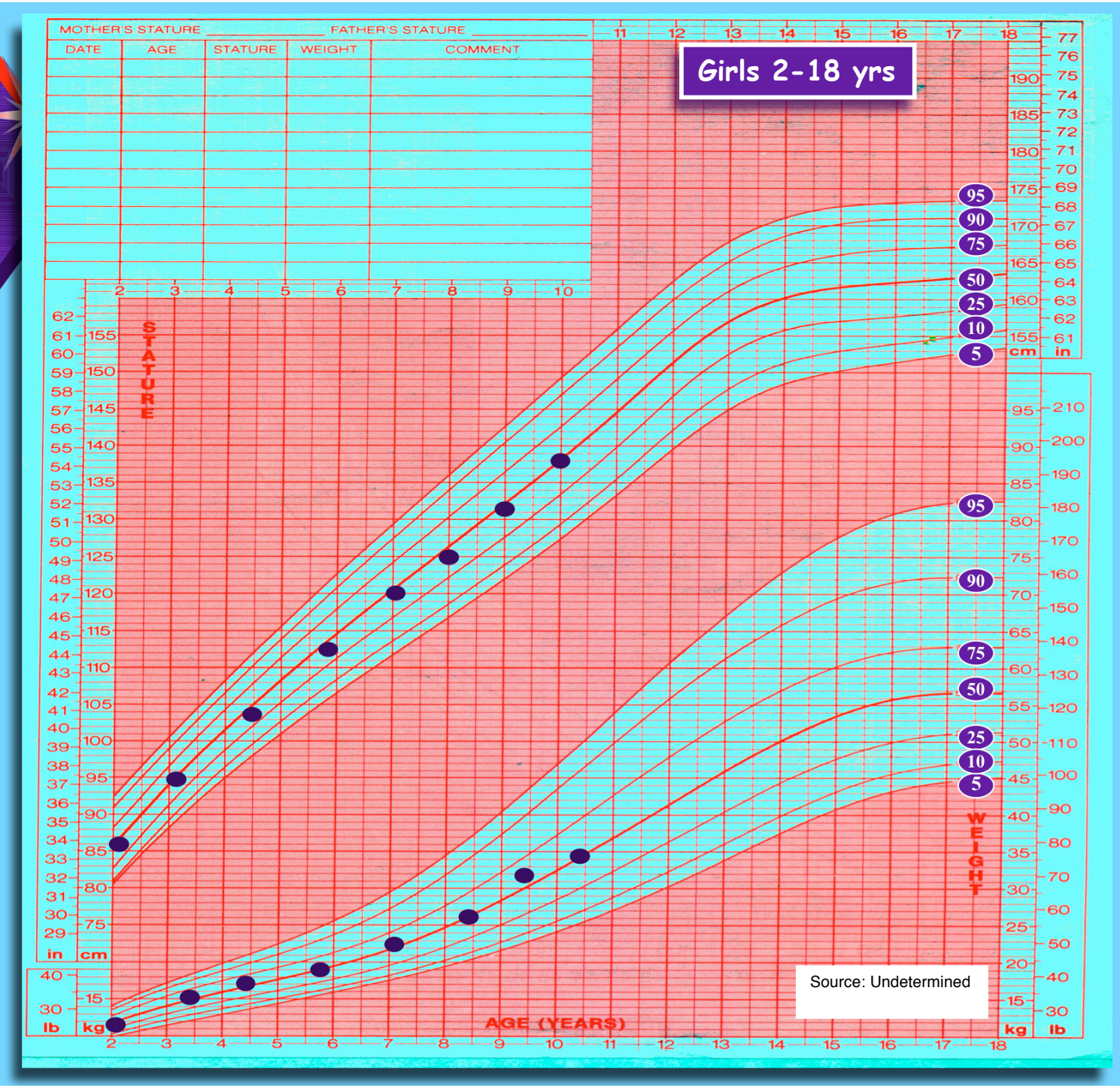
Upper / Lower Segment Ratio

Lower segment : symphysis pubis to floor
Upper segment : Ht (-) lower segment

Image of fetal and post-natal growth chart removed

2m 5m Birth 2yr 6yr 12yr 25yr

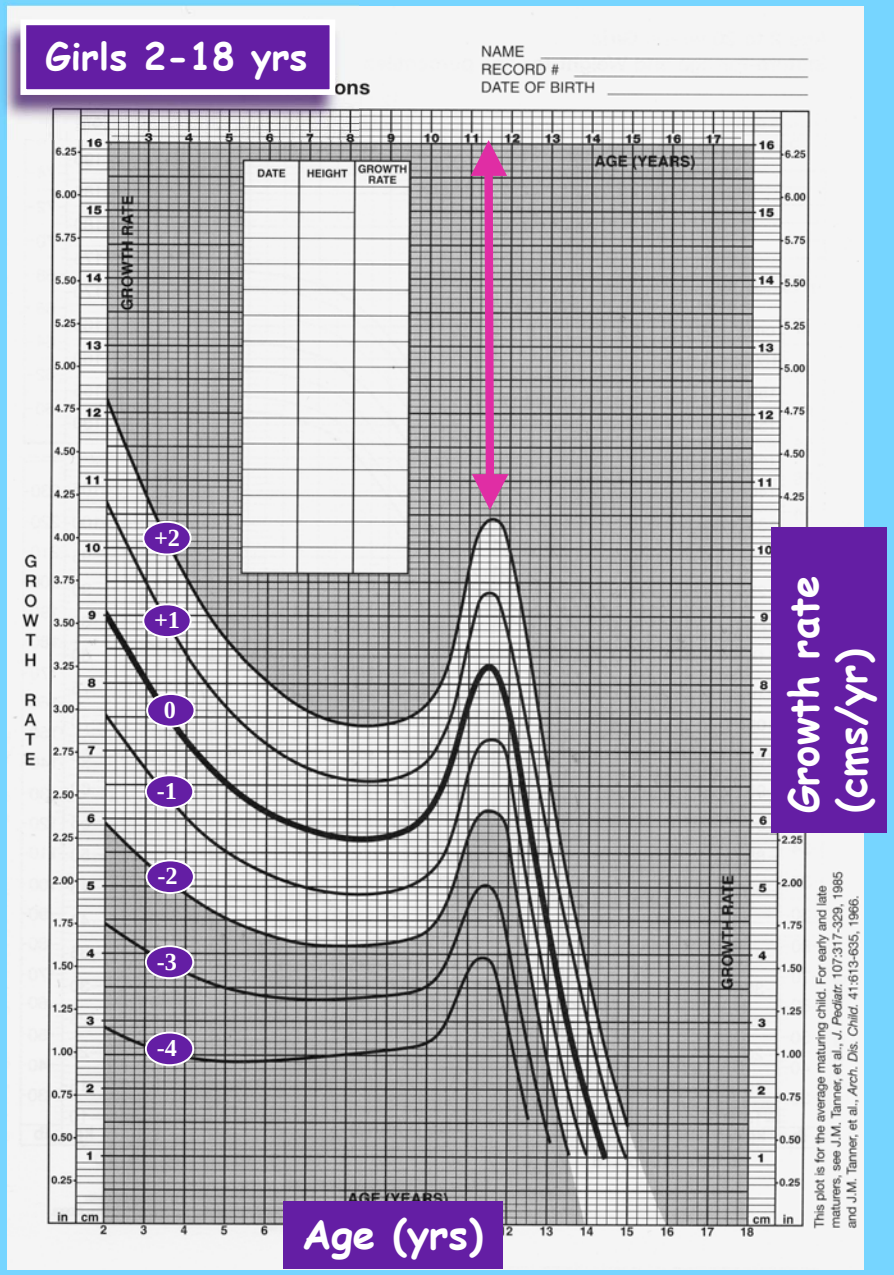
Fetal Post-natal


MOTHER'S STATURE
FATHER'S STATURE
DATE
AGE
STATURE
WEIGHT
COMMENT
Girls 2-18 yrs
STATURE
WEIGHT
AGE (YEARS)
95
90
75
50
25
10
5
in
cm
lb
kg
Source: Undetermined

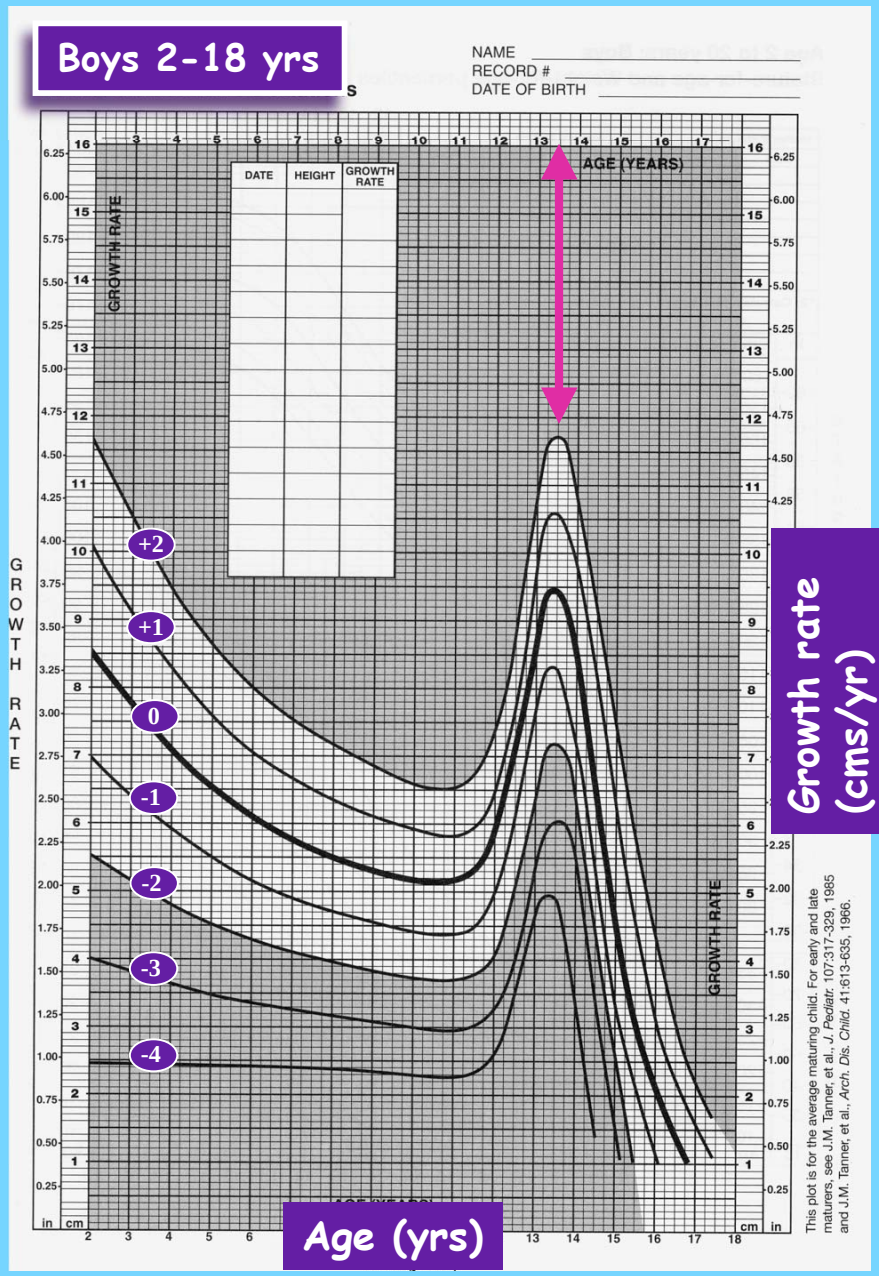
Normal Growth

Growth Velocity

- measured in cms/yr
- should be measured over at least a 6-12 month period
- more the # of height points used to calculate GV – more reliable is the interpretation
- assessment of pubertal status is critical for interpretation of GV
- Normal GV – is a strong argument AGAINST a significant hormonal abnormality



Source: JM Tanner, et al.



Source: JM Tanner, et al.

Normal Growth

- Chronological age
- Dental age
- Bone Age (skeletal maturation)

beyond the neonatal age – X-ray of L wrist

comparison with published standards (Greulich & Pyle)

Usefulness – prediction of final height

- age of onset of puberty closely linked to bone age
- corroborates diagnosis, but is never diagnostic

Caveats – imprecise / ethnic variability

SHORT STATURE

- Definition
- Classification
- Etiology
- Evaluation / Diagnostic Approach
- Treatment

SHORT STATURE Definitions

- Short Stature
  height < 3rd percentile
  - Growth Retardation
    growth velocity < 3rd percentile

SHORT STATURE

Definitions

- Short Stature
  - height < 3rd percentile
- Growth Retardation
  - growth velocity < 3rd percentile

Etiology

Normal Variant ⟷ Pathological

SHORT STATURE

Normal Variant

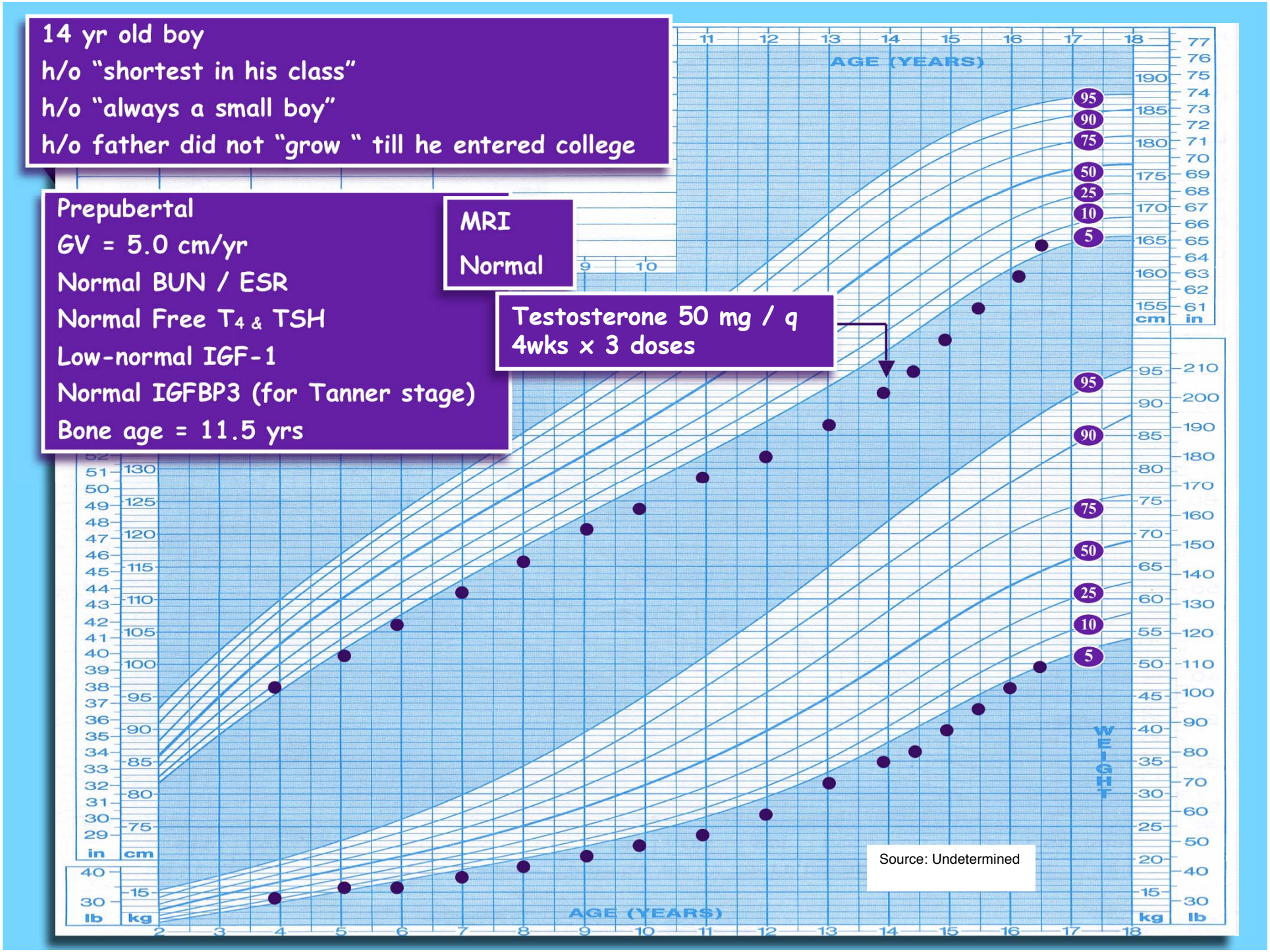
Familial / Genetic

final ht appropriate for parental ht
normal size at birth
GV may be ↓ in 0-3 yrs of age
BA = CA

Constitutional Delay of Growth & Puberty "Late Bloomer"

family history
normal size at birth
normal GV
delayed puberty
BA < CA

BA = bone age
CA = chronological age


14 yr old boy
h/o "shortest in his class"
h/o "always a small boy"
h/o father did not "grow " till he entered college
Prepubertal
GV = 5.0 cm/yr
Normal BUN / ESR
Normal Free T4 & TSH
Low-normal IGF-1
Normal IGFBP3 (for Tanner stage)
Bone age = 11.5 yrs
MRI
Normal
Testosterone 50 mg / q 4wks x 3 doses
AGE (YEARS)
WEIGHT
Source: Undetermined

SHORT STATURE

Definitions

- Short Stature
  - height < 3rd percentile
- Growth Retardation
  - growth velocity < 3rd percentile

Etiology

- Normal Variant
- Pathological
  - Proportionate
  - Disproportionate

SHORT STATURE

Pathological
Proportionate

Endocrinopathies

- Hypothyroidism
- GH deficiency
- Cushing's syndrome

GI

- Malabsorption
- Inflammatory bowel disease
- Celiac disease

Renal

- Chronic renal failure
- Renal tubular acidosis

Chronic Systemic Illness

- Cardiac
- Pulmonary
- Liver
- Infection

IUGR

Malnutrition

Psychosocial Dwarfism
Emotional Deprivation Syndrome

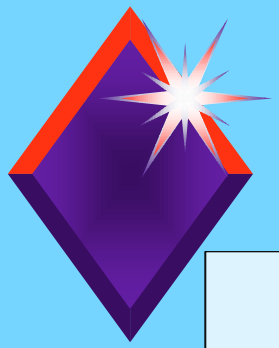


Image of one year old boy removed

Ht age = 1 yr old

Image of one year old boy removed

4 yr old boy

Voracious appetite / drinks urine – toilet bowl

Withdrawn / flat affect

No dysmorphic features

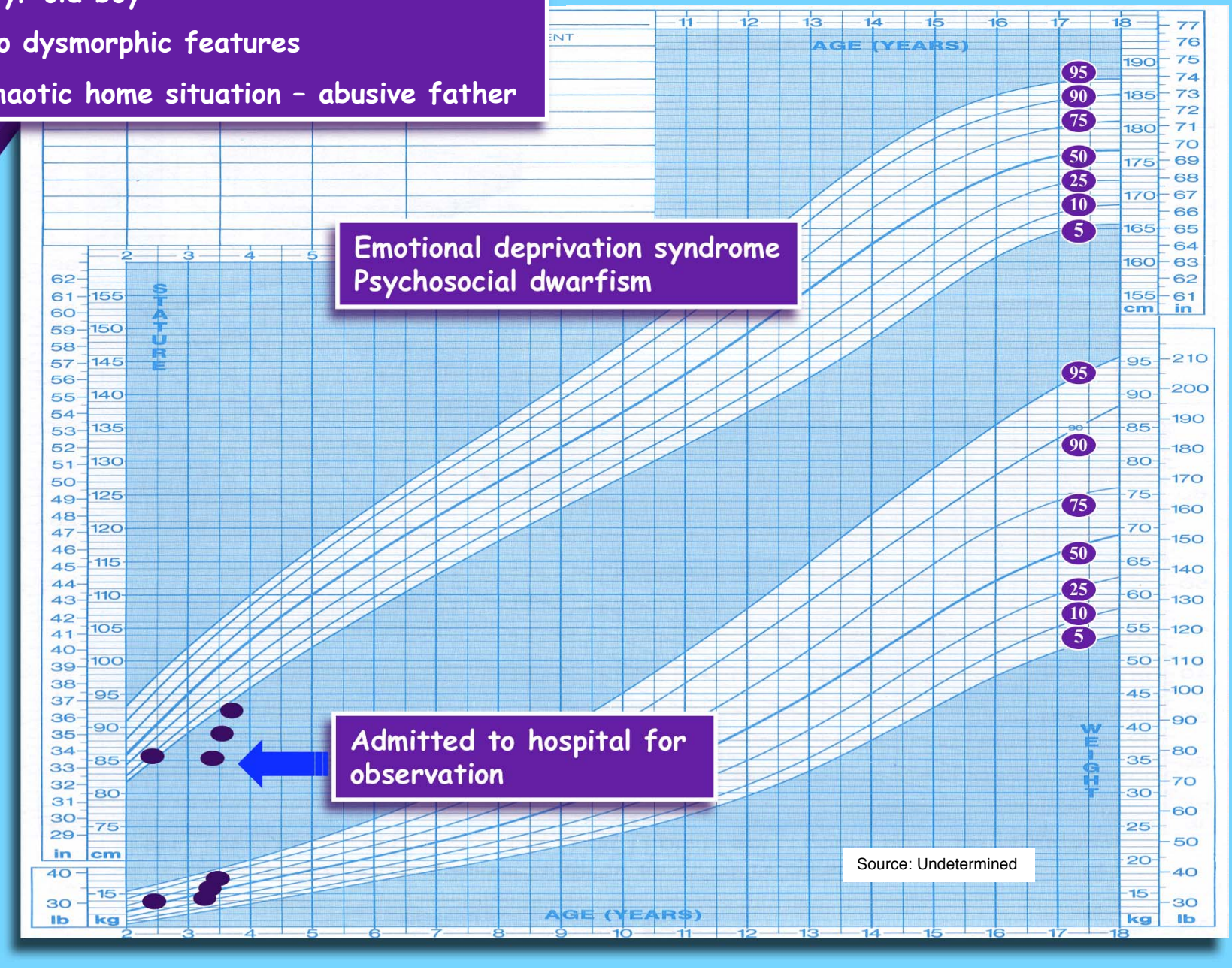
Chaotic home situation – abusive father

All lab tests normal

4 yr old boy

No dysmorphic features

Chaotic home situation – abusive father



Source: Undetermined

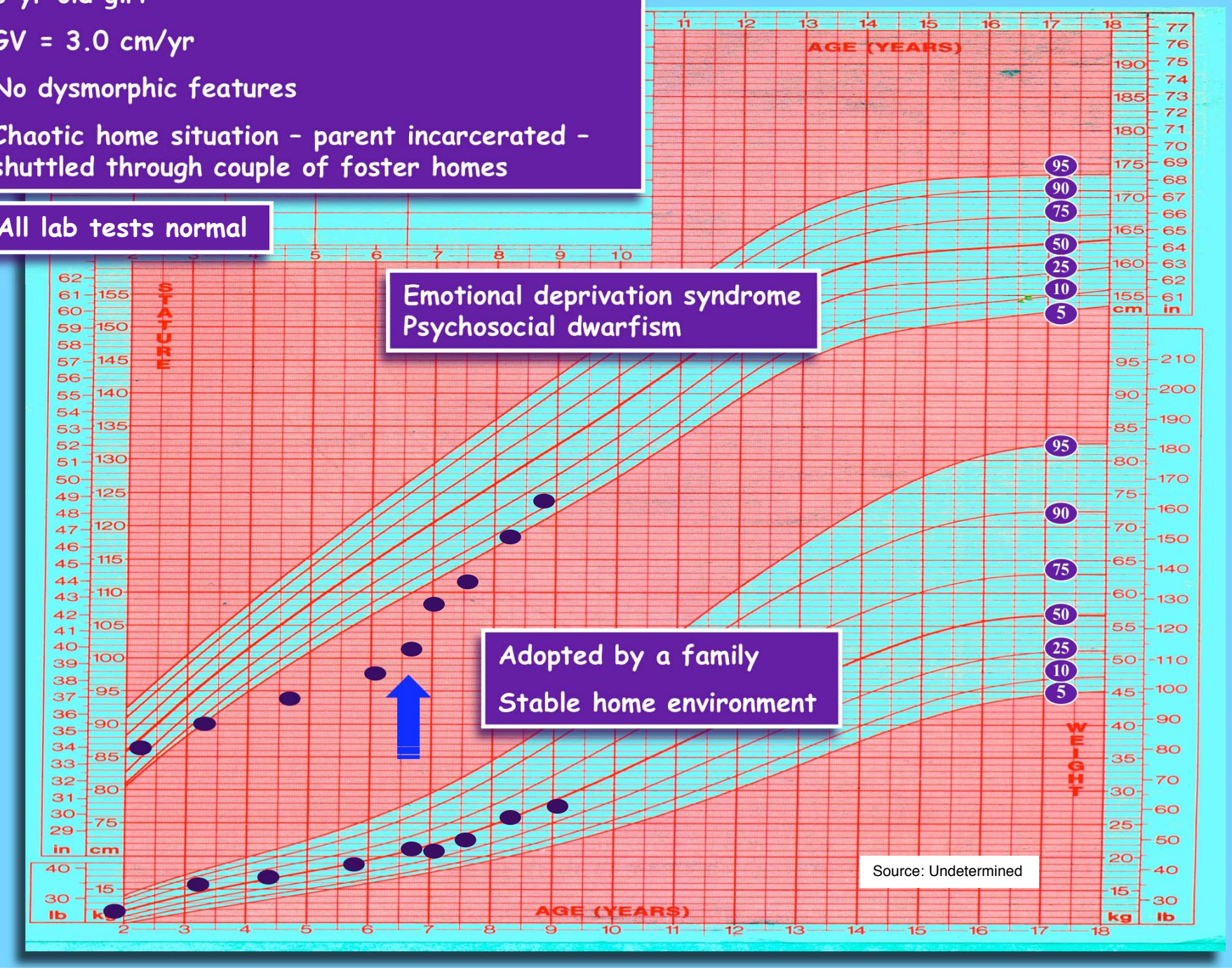
6 yr old girl

GV = 3.0 cm/yr

No dysmorphic features

Chaotic home situation – parent incarcerated – shuttled through couple of foster homes

All lab tests normal



Source: Undetermined

SHORT STATURE

Pathological
Disproportionate

Skeletal Abnormalities

- Dysplasia
- Achondroplasia
- Rickets
- Vertebral anomalies

Dysmorphic Syndromes

- Turner
- Down
- Russell-Silver
- Prader-Willi
- Pseudo-hypoparathyroidism

SHORT STATURE

Evaluation
Clinical History

Prenatal	maternal infection, alcohol
Pattern of growth	birth wt and length
Family History	onset of puberty
Nutrition	
Systemic Disease	
Drugs	steroids
Neurological	headache, vision, enuresis
Psychosocial	

SHORT STATURE

Evaluation
Physical Exam

Anthropometric — ht, wt, head circ., arm span, U/L ratio

Nutritional state

Tanner Staging for Pubertal Development

First sign of puberty on PE:
♀ breast dev / ♂ incr in testicular volume

Dysmorphic Features

Neurological exam

Thyroid Gland

SHORT STATURE

Evaluation
Diagnostic Approach

Target Height (in cms)

$$\text{girl} = \frac{[\text{father's ht} + \text{mother's ht}] - 13}{2}$$

$$\text{boy} = \frac{[\text{father's ht} + \text{mother's ht}] + 13}{2}$$

normal range is ± 8 cms

SHORT STATURE

Evaluation
Diagnostic Approach

Key Parameter - Growth Velocity

Normal GV

Familial
Constitutional

Impaired GV

Malnutrition
Chronic systemic illness
IUGR
Psychosocial
Chromosomal abnormalities
Endocrine
Malabsorption
Bone dysplasias

SHORT STATURE

Evaluation
Laboratory Tests

Screening Tests

CBC, ESR, BUN
FT_4, TSH
IGF-1, IGFBP3
Tissue Transglutaminase ab

KARYOTYPE
- in girls to exclude TURNER
- dysmorphic features

RADIOLOGICAL
- bone age
- skeletal survey

SHORT STATURE

Growth Hormone Deficiency (GHD)

SHORT STATURE

GH Deficiency (GHD)
Signs & Symptoms

- Neonatal – normal size / hypoglycemia / jaundice / micropenis / midline defect
- Decreased growth velocity
- Delayed dentition / mid-facial hypoplasia
- Increase in adiposity

SHORT STATURE

GH Deficiency (GHD) Causes

- Tumor - craniopharyngioma
- Trauma – surgery / irradiation
- Idiopathic
- Congenital Aplasia / Hypoplasia / Septic-optic dypslasia
- Genetic Defects –
  - Isolated Growth Hormone Deficiency (IGHD)
  - PROP1 / POU1F1 (*Pit1*)

SHORT STATURE

GH Deficiency Diagnosis

Criteria for diagnosing GH deficiency

Clinical (NOT laboratory) diagnosis

- GV < 2 SD
- Low IGF-1 & IGFBP-3
- Provocative GH Level < 7-10 ng/ml

Corroborative evidence

- Delayed BA
- Related pathology

SHORT STATURE

GH Deficiency
Diagnosis

Measurement of GH

- Spontaneous pulsatility of GH
  precludes random measurement
- Provocative test after overnight fast
  - Insulin induced hypoglycemia is the "Gold standard"

IGF-1 / IGFBP3

- Altered by nutritional status
- Normal range related to age & pubertal status

SHORT STATURE

Treatment
Indications for GH Therapy

- Growth hormone deficiency
- Turner syndrome
- Renal disease, before transplant
- Small for gestational age
- Prader-Willi syndrome
- Idiopathic short stature

SHORT STATURE

Treatment
GH Replacement Therapy

s/c injection
7days/wk

Side Effects

- Secondary/tertiary hypothyroidism
- Worsening of scoliosis
- Slipped capital femoral epiphysis
- Pseudotumor cerebri

Monitor

GV, Free T_4, IGF-1, IGFBP3

$8\frac{1}{2}$ yr old girl

h/o poor growth x 12-18 months

recent h/o vague headaches

school performance has recently deteriorated

recent episodes of enuresis

Prepubertal

GV = 1.5 cm/yr

Low Free T_4, Normal TSH

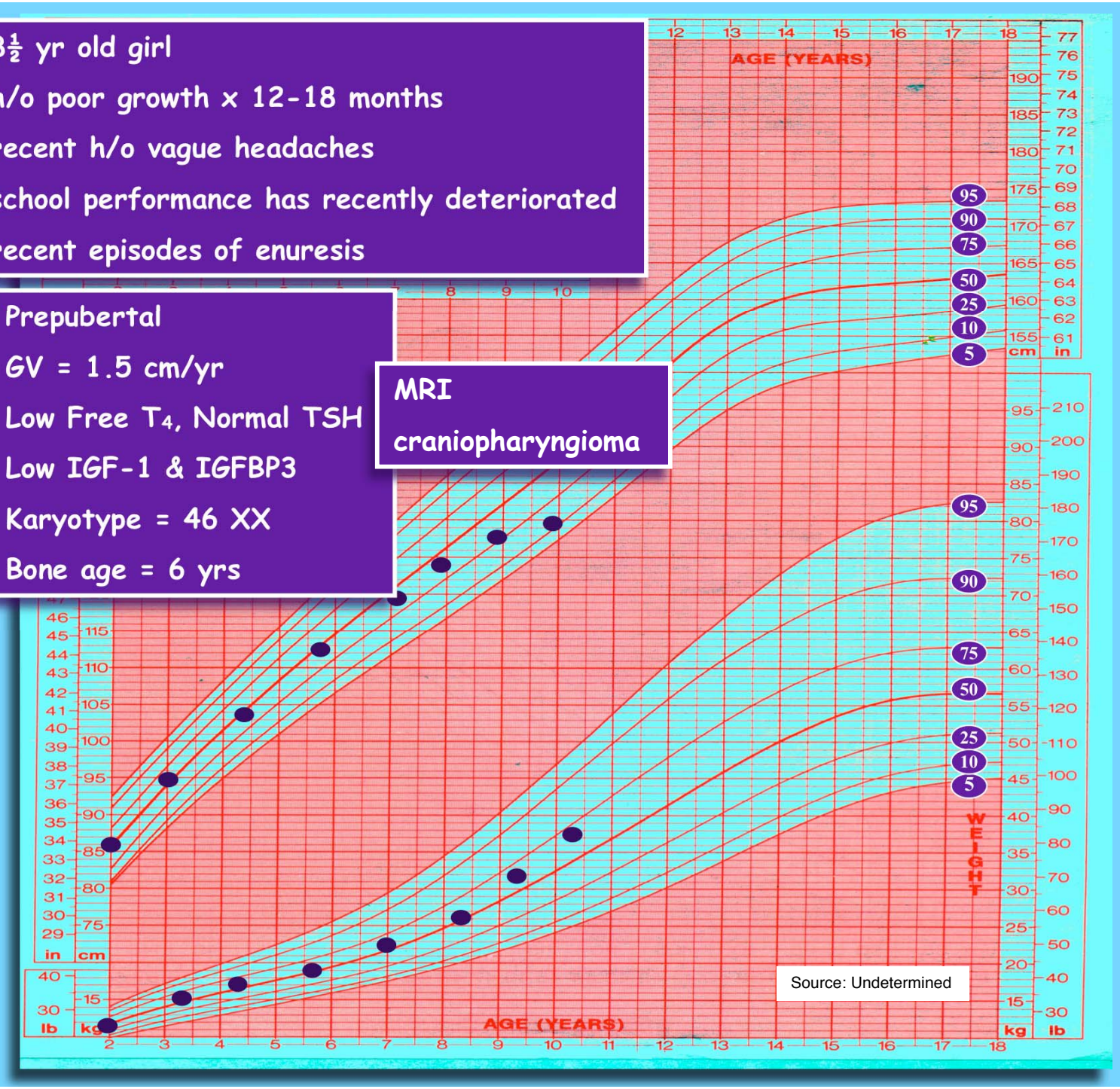
Low IGF-1 & IGFBP3

Karyotype = 46 XX

Bone age = 6 yrs

MRI

craniopharyngioma



Source: Undetermined

8½ yr old girl

h/o poor growth x 12-18 months

h/o vague abdominal discomfort

Prepubertal

GV = 2.5 cm/yr

Normal Free T_4 & TSH

Low IGF-1

Normal IGFBP3

Karyotype = 46 XX

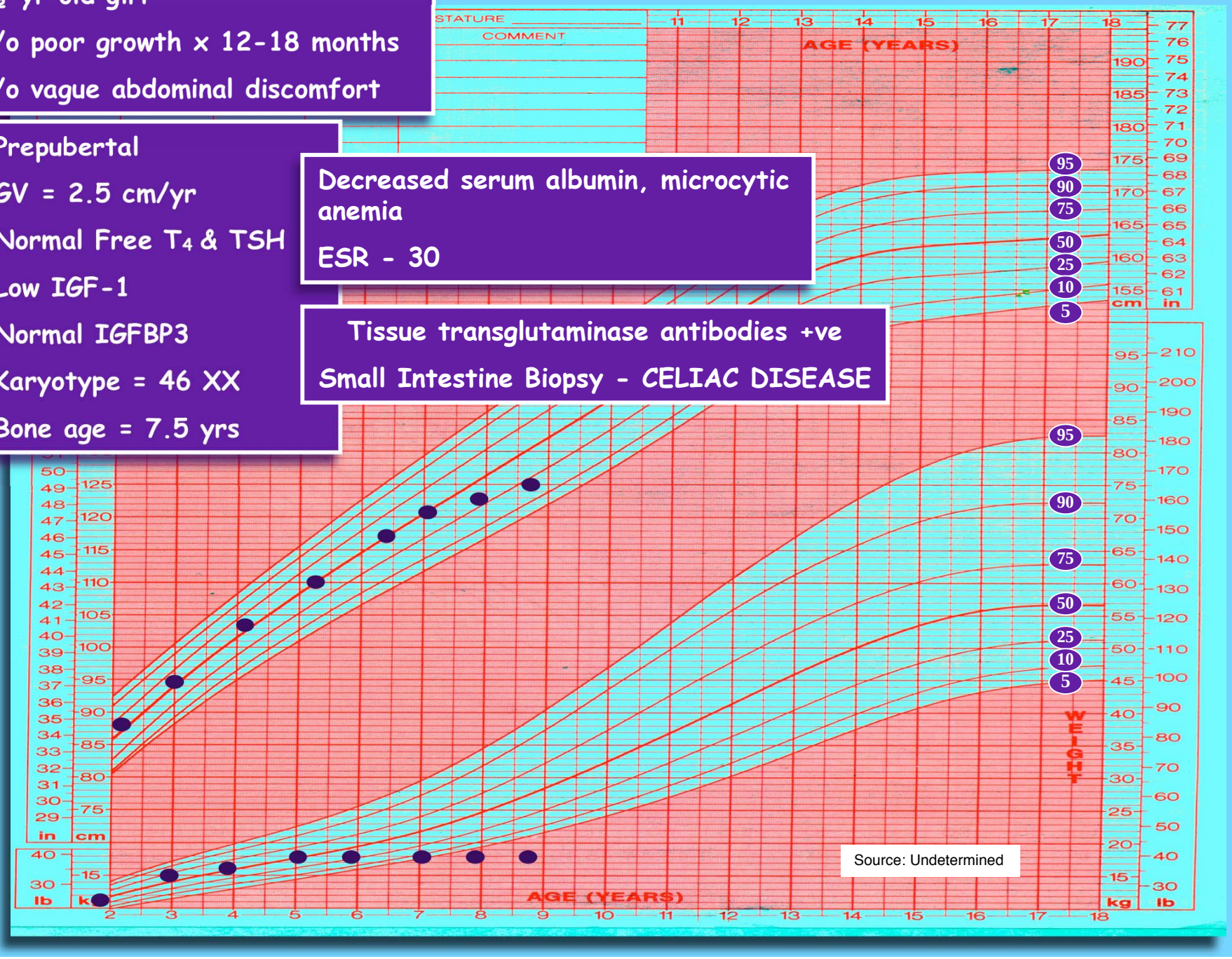
Bone age = 7.5 yrs

Decreased serum albumin, microcytic anemia

ESR - 30

Tissue transglutaminase antibodies +ve

Small Intestine Biopsy - CELIAC DISEASE



Source: Undetermined

5 yr old girl

GV = 3.0 cm/yr

subtle dysmorphic features - clinodactyly, webbing of neck ±, ↑ carrying angle

GV = 3.0 cm/yr

Normal Free T_4 & TSH

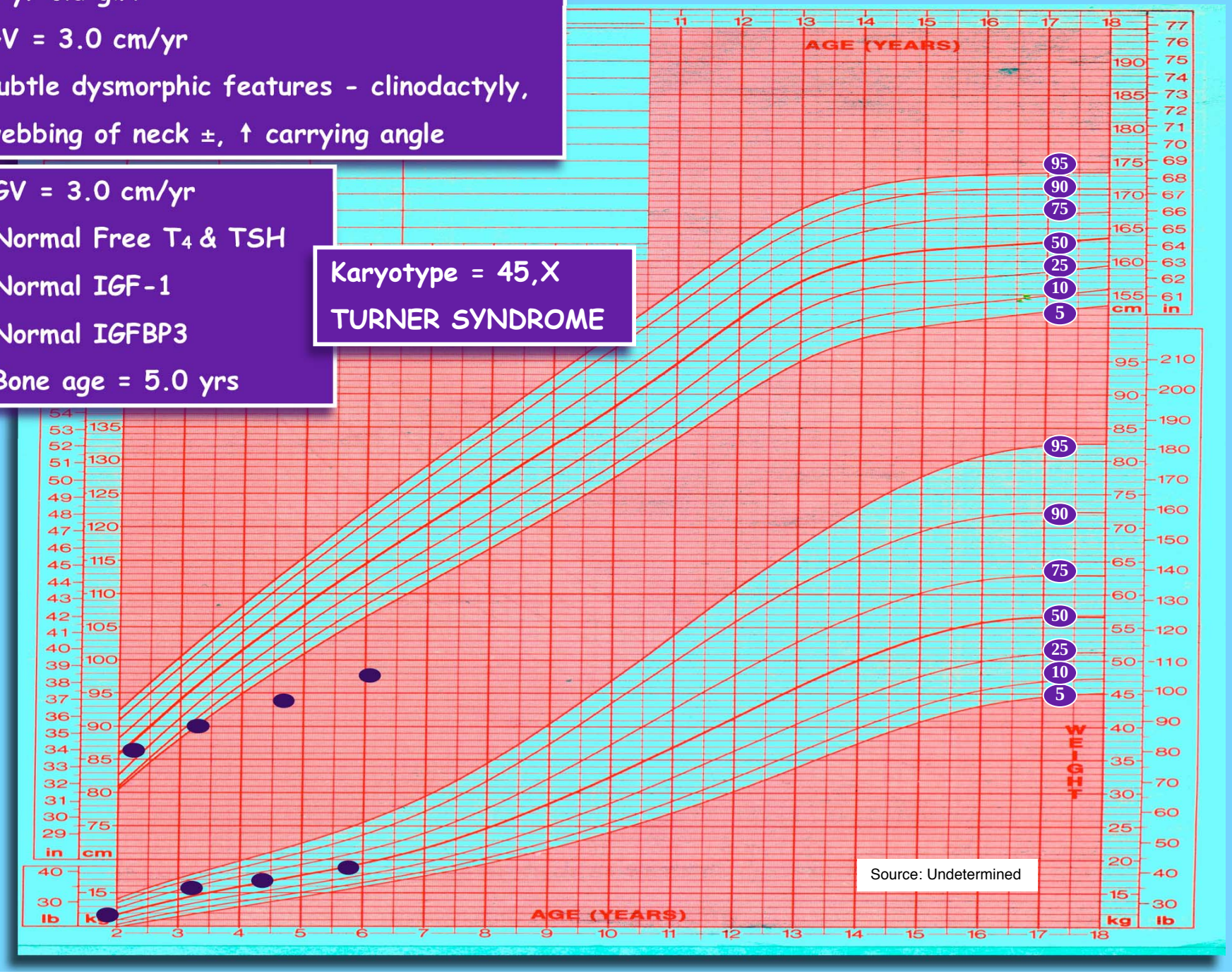
Normal IGF-1

Normal IGFBP3

Bone age = 5.0 yrs

Karyotype = 45,X

TURNER SYNDROME



Source: Undetermined

Turner Syndrome

Turner Syndrome

- Described in 1938 by Dr. Henry Turner
- Most common sex chromosomal abnormality in females -- X chromosome
- Frequency 1:1500 to 1:2500 in live born infant girls
- 15% of spontaneous abortions = TS

Turner Syndrome

Image of Turner Syndrome Karyotype removed

Karyotype 45, X

Turner Syndrome

Clinical Features – Postnatal

Growth Failure	80-100%
Gonadal Dysgenesis	80-100%
Inverted/ widespaced nipples	60%
Nail dysplasia	60-80%
High narrow palate	60-80%
Cardiac malformation	40-60%
Renal dysplasia	40-60%
Low hairline/webbing	30-40%
Pigmented nevi	common

Turner Syndrome

Turner Syndrome

Lymphedema

- Lymphedema at birth is highly correlated with 45,X karyotype and congenital heart abn

If you slept through this lecture…the 4 points to remember

- Growth velocity (and NOT height)

  is the key anthropometric parameter
- Normal growth velocity virtually

  excludes a pathological cause for short stature
- Always exclude Turner's synd in a girl with short stature
- Diagnosis of a child with growth problems is made more on CLINICAL and less on laboratory criteria