Challenges, successes and pitfalls of growth and development and GH therapy in Turner Syndrome

Case presentations that underscore some of the variance of growth response and growth trajectory in TS.

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Disclosures

Over the last 2 years I have:

• Received honoraria for pharmaceutical Nursing Advisory Board (one-off) for Pfizer, Sandoz, Merck EMD-Serono, Hoffman La Roche.

• I have been an invited speaker for Merck EMD Serono International IMAGE European Nursing Conference (October 2014).

• Using Hoffman La Roche/Genentech/CDC TS/regular growth charts in this presentation.

Objectives

2. Identify and review predictors of good growth hormone (GH) response in TS.
3. Identify and review predictors of poor GH therapy response in TS.
4. Compare and contrast literature findings of GH and growth response in TS.
Turner Syndrome (TS):

- About 1 in 2500 live female births is affected by TS.
- Implicated in 15-20% of all miscarriages.
- One of the more common genetic conditions.
- Complete or partial loss of one X chromosome.
- Short stature caused by haploinsufficiency of the short-stature homeobox-containing gene (SHOX) located within the Xp-terminal, pseudoautosomal region of the X chromosome. It affects virtually all individuals with TS.

**Short Stature Homeobox (SHOX) - Conditions Caused**

This disorder presents the MCP with a challenging array of genetic, developmental, endocrine, cardiovascular, otolaryngology, psychological and reproductive issues.

**CLINICAL PRACTICE GUIDELINE**

Case of Girls and Women with Turner Syndrome: A Guideline of the Turner Syndrome Study Group

Heathier Children, A Better World.

**Growth in TS**

Linear growth is attenuated in utero. Linear growth lags during childhood and adolescence resulting in mean final adult heights of 143cm (4 feet 8 inches) + 20 cm (8 inches) below the mean for the population.
Phenotypic features and conditions associated with TS

**Very Frequent >50%**
- Short stature
- Gonadal dysgenesis
- Recurrent otitis media
- Lymphedema of hands and feet
- Hyperconvex nails
- Narrow maxilla, dental crowding
- Micronothia
- Low posterior hair line
- Broad chest, wide spaced nipples
- Wide carrying angle
- Short fourth metacarpals
- Obesity

**Frequent <50%**
- Hearing loss
- Scoliosis, Kyphosis
- Pigmented nevi
- Elbowed neck
- Cardiac abnormalities
- Hypertension
- Hypothyroidism
- Glucose intolerance

**Occasional <5%**
- Osteopenia
- Hip Dislocation
- Inflammatory bowel disease
- Celiac disease
- JRA
- Liver disease
- Gonadoblastoma

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**Misinformation of effects of GH in TS**

"Human growth hormone is a standard part of treatment of Turner Syndrome (TS)."
"Today, it is considered a safe and effective way to reverse some of the signs of Turner Syndrome."

"The primary purpose of growth hormone is to regain height in girls with TS. Without growth hormone treatment, the average height of an adult woman with Turner Syndrome is 4 ft 8 in. In fact, girls who do not receive growth hormone are typically about 8 inches shorter than their predicted height would be with growth hormone."

"Growth hormone not only treats delayed physical growth but also delayed sexual development (another main feature of Turner Syndrome.)."
Cochrane Systemic Reviews of GH tx in TS

- 4 RCTs (n=211)
- Recombinant human growth hormone (hGH) doses between 0.3 - 0.375 mg/kg/wk
  - Increase short-term growth in girls with Turner Syndrome (TS)
  - Approximately 3 cm in the first year of treatment.
  - And by approximately 2 cm in the 2nd year of treatment.
- The FAH of treated women was still outside the normal range (more than 2SD below the normal population mean).

Cave CB, Bryant J, Milne R. Cochrane Database Syst Rev. 2003(1):CD003887

Subsequent review in 2007 noted similar results with 4 RCT's (n=365)
- (same findings as above)
- It does appear that initial growth improvements decline over longer treatment periods
- Recommended additional trials to be carried out with control groups until FAH to allow better informed decisions about whether the benefits of hGH treatment outweigh the requirements of treatment over several years at considerable cost

C. Bryant, C. Cave, O. Milne. Cochrane Database Syst Rev. 2007: Jan 24(CD003887)

Favourable GH growth response in TS is influenced by...

- Early diagnosis
- Karyotype
- Taller stature at GH start
- Increased growth response in 1st year of therapy
- Taller parents
- Absence of other disease
- Adherence to therapy
**Current Canadian Practice:**

Approved by Health Canada.
- GH stimulation testing not required in Canada.
- GH offered to all TS girls.
- Initiation of tx at 2-6 years of age, or when GV declines, or at dx if older.
- Dosing: 0.05mg/kg/dose, 6 days/week (0.3mg/kg/week).
- Treated until FAH or BA of 14 years and/or GV actual or projected < 2 cm/year.
- Puberty induction ~ 12 years of age (oral/transdermal) for those that require it.

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**Case Study:**

A 4.5 year old, short stature, female child was referred for evaluation of short stature. The mother had a previous history of GH use. She was brought to the attention of the pediatrician at 6 years of age due to slow growth. She had a history of hypothyroidism in her mother and a family history of OM. She was referred to her pediatrician...

**Phenotypic stigmata of TS:**
- Epicanthal folds,
- Ptosis,
- Short webbed neck, low posterior hairline,
- Outstanding and anomalous ears (left anteriorly curved),
- Wide spaced nipples (16 cm), and
- Moderate pectus excavatum,
- Grade 4 systolic ejection murmur,
- Scoop nails.

Clinical dx of TS made, confirmed with Karyotype.

Normal Renal function and U/S, TFTs, IGF-1 lowish.

Large ASD secundum on Cardiac assessment.

Required cardiac sx 6 mos after Cardiac surgery initiated GH.

Karyotype 45X

Started GH at 4.5 yrs (2006) following cardiac surgery.
Dose of .05 mg/kg/dose (0.3mg/kg/week).
Ht 97.1 cm and wt 14.1 kg.
First year on GH:
- 9.9 cm of growth, excellent response.
- No SE.
- TSH 3.16, Free T4 18.7, anti-TPO <10,
IGF-1 148 (48-130).

8 yrs of active (prepubertal) treatment with good adherence, crossed numerous centiles.
25th centile regular growth curve (4.5 cm, 7 cm, 8 cm, 5.2 cm, 6.7 cm).

4.5 yrs SDS -2.37
12.5 yrs SDS -0.65
Spontaneous Puberty in Turner Syndrome...

The incidence of spontaneous puberty in TS:

- Reported to be about 1/3 (12-40%) esp. in mosaic karyotypes.
  - streak gonad with accelerated oocyte degeneration
  - Increased stromal fibrosis
  - Only a small percentage will have spontaneous menarche,
  - Eventual gonadal failure in 90%
  - Spontaneous pregnancies are rare (2-5%)

References:
- Mortensen KH et al. (2010). Obstet Gynecol 115: 446-449
Spontaneous Puberty in Turner Syndrome...

Italian retrospective multicenter study:
- 522 girls with TS >12 yrs of age
- 84 (16.1%) had spontaneous onset of puberty with menarche at 13.2 +/-1.5 yr
- GH treatment does not seem to exert any influence on either the age of onset or the prevalence of spontaneous puberty

Precocious Puberty in Turner Syndrome

- Precocious puberty in TS patients is rare.
- To date, only five cases have been reported in the literature, four of them showing mosaic TS and one a karyotype with structural abnormality of one X chromosome.
Breast Development in TS

Shield / Broad Chest
Wide spaced nipples
Poor Breast Development

Hypoplastic and tubular breast development

Normally:
- Breast bud responds to estrogen.
- The action of estrogen depends upon the presence of GH to stimulate production of IGF-I in the mammary gland.
- Skin envelope passively stretches in response to stimulated growth.
- Tanner staging

In tubular and or hypoplastic breasts:
- Tight fibrous mesenchymal layer resists growth in any or all of the breast quadrants, except at the areola (an area of low resistance).
- Atrophy of periareolar skin results in more stretching and results in tubular shaped breast with a large areola.

Breast development in TS

- Paucity of medial and inferior skin
  - Inner quadrant tightness (areolas face in)

Implications for TS:
- Poor breast development is not uncommon in TS
- May be problematic to use breast development to stage pubertal development with or without use of ovarian hormone replacement.
- Breast and chest wall anatomy in TS may make it more difficult to differentiate breast staging (Tanner).
- Poor breast development has psycho-social implications for women.
- Breast augmentation/Plastic Surgery may be indicated, recommended and covered in TS.
Karyotype 45X/46X Del 22.2.31
• Mom has TS, same karyotype (4'11")
• Required IVF, M obese, MPH 5'0" (?)
• Behavioural issues, DD, ADD/ADHD, ?Autism spectrum
• Short webbed neck,
• Low posterior hairline
• Wide spaced nipples
• Shortened arms – wide carrying angle
• Started GH just after 8yrs (0.05 mg/Kg/dose)

IGF-1 135 (48-350)
BMI 45.5
8yrs SDS -1.25
15 yrs SDS -1.31
Excellent GV, first yr 10+cm (50centile)
9 yrs, BA 11 yrs
IGF-1 596 (40-446ug/L)
10yrs 10 mos, BA 12-13 yrs
IGF-1 780 (88-691/691ug/L)
GH unchanged from start (0.05mg/kg/dose)
Over time…
↑ Obesity
↑ IGF-1's
↑ Disproportion (shortened arms, size 9.5 feet)
Referrals to community Dietician, wt management programs, SW, psychiatrists.
Spontaneous puberty
Menarche 11.5 years
LH 2.5, FSH 3.1, Estradiol 157
IGF-1 802 (120-691/1096ug/L)
At 12 yrs 2 months 84.1kg DH d/c'd at 12.5 years

Obesity…
What the literature says:
• Women with TS were more obese compared with women with a normal karyotype.
• Obese TS patients had higher serum triglyceride concentrations.
• More likely to be hypertensive.
• Hypertension was independent of obesity and may be under-recognized because of failure to compare with age matched normal ranges.

Supraphysiologic IGF-1 Levels

- IGF-1 is the major mediator of the anabolic and growth-promoting effects of growth hormone (GH):
  - Transported by IGF-binding proteins, in particular IGFBP-3
  - Highly age dependent and results must always be interpreted within the context of the patient’s age.
  - IGF-1 is produced in large amounts in the liver as well as in adipose tissue
  - The aim of both pediatric and adult GH replacement therapy is to achieve IGF-1 and IGFBP-3 levels within the reference range, ideally within the middle-to-upper third.


Disproportionate Growth in TS

Body proportions of untreated girls with TS compared to healthy girls, relative to height:

- More coarse and stocky body habitus
- Larger trunk, hands and feet
- Relatively short lower extremities
- Relatively broad shoulders and pelvis


"Ideally, prolonged exposure to elevated IGF-I levels should be avoided because of theoretical concern about potential long-term adverse effects"
Disproportionate Growth in TS

The increase in height after long term GH treatment is accompanied
- By an even larger increase in foot size and
- A moderate improvement of the disproportion between height and sitting height.
- In the last phase of growth, some girls the study complained about big feet.
  - The possibility of additional foot growth may have influenced their decision to discontinue GH treatment before adult height was reached.


Karyotype 45X/46X i(X) (q10) -mosiac
- BA failure
- Wide spaced nipples
- Later: SNHL - bilaterally - hearing aids
- DD
- Started GH: 2 y/o

Adherence
- Poor adherence to GH is common (5-80%)
- Efficacy of GH tx is based on adherence.
- Adherence rates not generally associated with:
  - Age
  - Cause of GH treatment
  - Socioeconomic status
  - Person who administered the injections
  - Type of injection device
  - GH product

Factors Affecting Adherence to GH Therapy

Barriers to GH therapy adherence in paediatric patients may include:

• Medication issues (e.g. apparent ineffectiveness, inadequate supply and side effects)
• Scheduling issues (social convenience)
• Cognitive/emotional issues (e.g. forgetfulness, preoccupation, lack of understanding of condition or instructions, lack of symptoms, fear of needles, poor tolerability and inadequate family support).
• Additional barriers in adolescence may include: denial, peer pressure and reluctance to seek medical advice.


Factors Associated and Not Associated with Adherence

<table>
<thead>
<tr>
<th>Factors associated with poor adherence</th>
<th>Factors not associated with adherence</th>
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<td>• Do not want to continue</td>
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“Factors specifically associated with poor adherence to GH therapy in observational studies are listed in table; notably, several factors have been associated with poor adherence in some studies but not in others”.


Scoliosis

• General incidence of scoliosis in general population is 2-3%.
• Girls with TS have higher risks for scoliosis and kyphosis
• 10-20% of girls with TS develop scoliosis, and kyphosis

Australian study:
• The 30% incidence in Turner syndrome was noted to be much higher than previously reported (11-12%).


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Slide 12
Thoracic dextroscoliosis with a Cobb angle measuring 66° from T5 to L1.

Lumbar levoscoliosis with a Cobb angle measuring 23° from L2 to L5.

3 years later. Again seen is a short segment dextroscoliosis of the thoracic spine measuring 79 degrees from the superior T6 endplate through the inferior T12 endplate.

8.2 yrs SDS - 4.78
17 yrs SDS - 5.37

Karyotype 45X dx at birth
MPH unknown
Foster Care
TS stigmata ++
Coarctation, repaired
Horseshoe Kidney, -vesicoureteral reflux
Congenital diaphragmatic hernia
Lymphedema (hands and feet)
Lt ptosis
DD, SLP, OT, PT
Scoliosis @ 7 yrs:
GH stimulation test
(25.6 ug/L Arginine, 12ug/L Clonidine)
Started GH @ 8.1 years
BA 6 yrs 10 mos
Initiated OHR at 14 yrs
BA 11 yrs
Menarche 15.5 yrs
GH d/c'd at 15 yrs.
Posterior spinal fusion @ 15.5 yrs.
Summary

- TS is a complex mix of complete and mosaic karyotypes that all have very individual phenotypic expression.
- Growth and development in TS is an unfolding story.
- GH potentially provides 1 additional cm of growth for every year of use.
- Adverse events are minimally reported.
- Poor pubertal growth velocity has a significant impact on FAH in TS.
- Clinicians need to be keenly aware of the many factors that impact growth and development in TS.
- Be conservative in growth predictions prior to and while on GH therapy.

Thank you!