

Workshop on Turner syndrome

How can very early treatment start and/or GH dosing based on IGF-I titrating improve treatment outcome in young Turner women?

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The chairmen of the workshop, Paul Saenger, USA and Claus Gravholt, Denmark, welcomed participants to this opportunity to design improved care for girls and women with Turner syndrome.

Lars Sävendahl, Sweden, talked about the importance of early diagnosis of TS. Nearly all girls with TS have short stature. However, in many affected girls the diagnosis of TS is not made until late childhood or adolescence (*Fig. 1*). TS is due to an abnormal or missing X chromosome. One of the most common chromosomal disorders, TS affects about 1 in 2000 to 2500 live-born female infants. Many of these infants are recognizable at birth, especially those with a 45,X karyotype. In the infant, TS may be suggested by lymphedema, dysmorphic features, or cardiac abnormalities. In fact, lymphedema is the key to diagnosis in most girls diagnosed with TS in infancy (97%). In contrast, short stature is the key for most girls diagnosed in childhood or adolescence (82%). In adolescence, the combination of growth failure and pubertal delay suggests the possibility of TS. Additional features permitting early

diagnosis include webbed neck, nail dysplasia, high palate, short fourth metacarpal, or coarctation (Sävendahl. *J Pediatr* 2000) (*Table I*).

In adulthood, an evaluation for infertility or amenorrhea may diagnose TS. Establishing an early diagnosis permits counseling about the phenotypic characteristics of TS; screening for cardiac, renal, thyroid, and auditory abnormalities; and testing for potential psychosocial or intellectual consequences of TS. These problems, if not appropriately addressed, may result in increased morbidity and reduced quality of life (Saenger. *J Clin Endocrinol Metab* 2001). Early diagnosis permits early GH therapy.

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Abbreviations:

GH	Growth hormone
GHD	GH deficiency
IGF-I	Insulin-like growth factor-I
IGFBP-3	IGF-binding protein-3
ISS	Idiopathic short stature
RR	Relative risk
TS	Turner syndrome

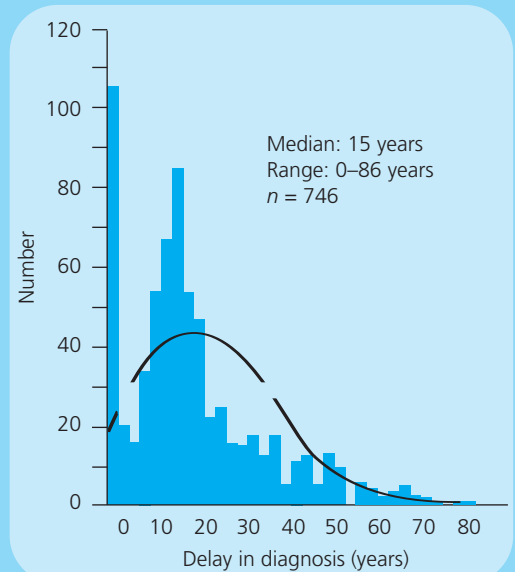


Figure 1: Delay in diagnosis from birth. From: Gravholt CH. *Eur J Endocrinol* 2004;151:657-87.

Table I: Clinical features of TS (according to age at diagnosis) occurring in 50% in one of the age groups. Adapted from: Sävendahl L. *J Pediatr* 2000;137:457.

Clinical features	Childhood (n = 24)	Adolescence (n = 15)	Infancy (n = 33)	Prenatal (n = 9)	All patients (n = 81)
Early growth failure (<5th percentile by age 4 yrs)	83%	47%	79%	75%	73%
Recurrent otitis media	71%	73%	94%	71%	81%
High-arched palate	70%	53%	84%	57%	71%
Delayed puberty	60%	66%	93%	0%	75%
Nail dysplasia	57%	80%	90%	57%	75%
Low-set ears	56%	58%	73%	40%	63%
Retrognathia	56%	36%	67%	33%	55%
Learning difficulties	55%	30%	52%	33%	48%
Cubitus valgus	53%	50%	52%	0%	47%
Feeding problems	43%	14%	56%	25%	40%
Strabismus	43%	23%	33%	0%	32%
Epicanthal folds	41%	31%	44%	83%	44%
Low posterior hairline	39%	75%	76%	13%	57%
Multiple nevi (>40)	35%	77%	41%	17%	44%
Webbed neck	26%	28%	73%	13%	44%
Short fourth metacarpal	25%	50%	37%	0%	33%
Ptosis	20%	25%	52%	17%	33%
Lymphedema as newborn	18%	14%	97%	22%	51%

TS specific growth standards have improved our ability to evaluate growth in young girls with TS. Most of the adult height deficit in TS is due to growth retardation during intrauterine life and during the first 3 years of life. Height deficit is -0.68 SD at birth, -1.6 SD at 1 yr, -1.8 SD at 2 yrs, -1.95 SD at 3 yrs, and -2.9 SD at 5 yrs (Davenport. *Horm Res* 2002). TS should be considered in girls with early growth deceleration. Early diagnosis of TS enables initiation of GH treatment before the height falls far below normal. Early GH therapy permits normalization of height during childhood and attainment of normal adult height. In addition, early GH therapy and taller height will often permit initiation of estrogen therapy at a normal age during adolescence. Optimal treatment of the girl with TS should begin with making the correct diagnosis at the earliest possible age. The pediatric provider should perform karyotype analysis in *all* girls with unexplained short stature, delayed puberty, webbed neck, lymphedema, or coarctation of the aorta (Table II).

Andrew Zinn, USA, discussed genotype-phenotype relationships in TS. TS is the phenotype of monosomy X or absence of the second sex chromosome. TS features include high intrauterine lethality, and among live-born girls, those features in Table I. In normal girls, most of one X chromosome is inactivated. However, genes near the tip of Xp, in the so-called 'pseudoautosomal region', escape X inactivation, and thus have diploid dosage in normal girls. The TS phenotype results from haploinsufficiency, or half-normal dosage, of those X-linked genes that escape inactivation. Rare girls missing only part of the second X show essentially the same spectrum of phenotypes as live-born 45,X TS girls. From karyotype-phenotype correlations in girls

with partial deletions, most TS genes are located on the short arm of the X chromosome (Xp).

Deletions of the pseudoautosomal region are associated with short stature and nonverbal learning disabilities, but few other TS stigmata. Large deletions of either the short or long (Xq) arm are associated with varying degrees of ovarian failure, implicating multiple disparate X-linked genes. Genes important for intrauterine viability are situated in Xq.

Karyotype-phenotype correlations have permitted identification of specific TS genes. One such pseudoautosomal TS gene, SHOX, is the major TS growth determinant. SHOX mutations are also implicated in two Mendelian growth disorders. Heterozygous mutations cause Leri-Weill dyschondrosteosis (Ross. *J Clin Endocrinol Metab* 2001), and

Table II: Guidelines for screening for TS. From: Sävendahl L. *J Pediatr* 2000;137:458.

Any girl with one or more of the following*

- Unexplained short stature (height <5th percentile)
- Webbed neck
- Peripheral lymphedema
- Coarctation of the aorta
- Delayed puberty

or

Any girl who has at least two or more of the following

- Nail dysplasia
- High-arched palate
- Short fourth metacarpal
- Strabismus

*Other suggestive features include a nonverbal learning disability, epicanthal folds, ptosis, cubitus valgus, multiple nevi, renal malformations, bicuspid aortic valve, recurrent otitis media, and need for glasses.

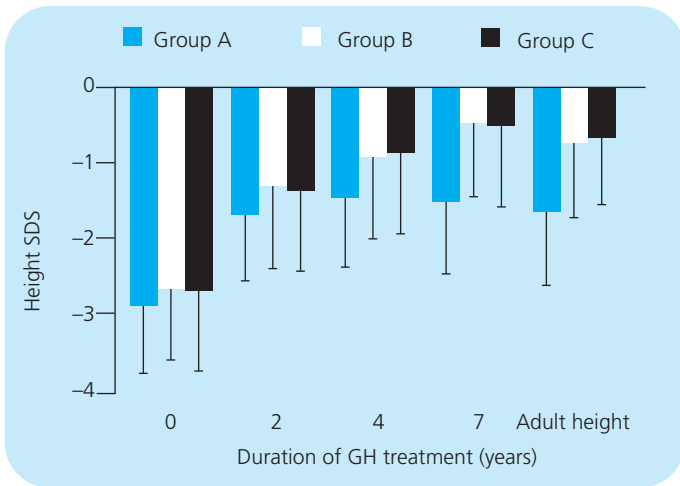


Figure 2: Height SDS during GH treatment. Group A dose: 4 IU/m²/day (0.045 mg/kg/day); Group B dose: same initial dose for 1 yr, then 6 IU; Group C dose: 8 IU/m²/day. From: Van Pareren Y. *J Clin Endocrinol Metab* 2003;88:1119–25.

homozygous mutations cause Langer mesomelic dysplasia. SHOX overdose leads to tall stature. A gene for TS nonverbal learning disabilities (impaired visuospatial abilities, nonverbal memory, motor function, executive function, attentional abilities) is probably also located in the pseudoautosomal region (Ross. *Am J Hum Genet* 2000 and Ment Retard Dev Disab Res Rev 2000). Mutation of the BMP15 gene, in proximal Xp, is a rare cause of ovarian failure. Finally, a ribosomal protein gene, RPS4X, is a candidate for an Xq viability gene. Molecular cytogenetic and genetic studies include new microarray-based techniques for detecting deletions at single-gene resolution. These, along with phenotypic correlation and genomic studies cataloging X-linked genes that escape inactivation, should allow the identification of additional TS genes in the near future (Zinn. *Semin Reprod Med* 2001).

Ron Rosenfeld, USA, introduced the concept of GH dosing in TS girls based on titration of IGF-I. Twenty years of experience with GH therapy in TS have shown a beneficial effect of GH therapy on growth, adult height, and probably bone mineral (Neely. *J Clin Endocrinol Metab* 1993). However, optimal GH dosing in TS has not yet been determined (Fig. 2). Several factors contribute to the complexity of GH dosing in TS:

1. patients are neither GH deficient nor IGF-I deficient at baseline;
2. responsiveness to GH, while dose-dependent, does not equal that observed in GHD;
3. estrogen therapy may impact responsiveness to GH;
4. variability of body mass index in TS renders weight-based paradigms problematic.

There is considerable variability in both growth and IGF-I responsiveness to GH therapy in TS. Serum IGF-I may vary from below the mean to above +3 SD for age. Given the key role of IGF-I as the major mediator of

postnatal GH-dependent growth, serial determination of serum IGF-I and IGFBP-3 may permit GH dose-titration. In a prospective, randomized trial, children with GHD or ISS (with moderate to severe IGF-I deficiency) were randomized to conventional, weight-based GH dosing or to GH dose titration arms designed to maintain serum IGF-I concentrations at 0 or +2 SD. GH dosages required to maintain IGF-I concentrations at 0 SD varied from 9–114 µg/kg/day (mean 33 ± 17). GH doses required to maintain IGF-I at +2 SD varied from 20–346 µg/kg/day (mean 110 ± 70), compared to the conventional GH dosage of 40 µg/kg/day.

These studies underscore the dramatic variability in GH responsiveness observed in GHD and ISS patients treated with GH, and demonstrate the feasibility of IGF-I-based GH dose titration. The potential utility of this approach in TS warrants evaluation, while protecting against IGF-I excess.

The fourth speaker, Claus Gravholt, Denmark, reviewed epidemiological, endocrine and metabolic features, and physical abnormalities (Gravholt 2004). TS is usually associated with reduced adult height, gonadal dysgenesis, low female sex steroid levels, and infertility. RR for thyroiditis is 16.6 (range 3.4–48.5, compared to 1.0 in normals), for type 1 diabetes 11.6 (5.3–22), type 2 diabetes 4.4 (2.4–7.7), hypertension 2.9 (1.2–6), and osteoporosis 10.1 (2.2–30.9). Metabolic syndrome is also common in TS adults. Aortic dissection may be the most serious health problem (>70 compared to 5.9 per 100,000 in controls). Morbidity and mortality are increased (RR 4.2, 3.2–5.4). Average intellectual performance is within the normal range.

Treatment with GH during childhood and adolescence allows a considerable gain in adult height. However, long-term consequences of GH treatment require evaluation. Puberty must be induced in most

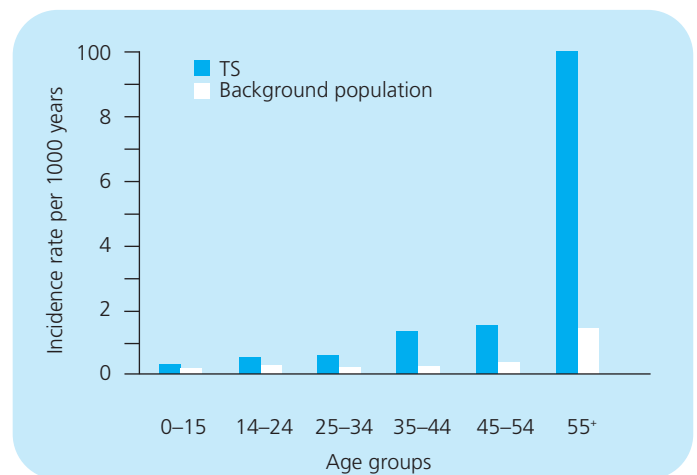


Figure 3: Overall fracture risk in TS by age groups, illustrating an increased risk of fractures in all age groups. From: Gravholt CH. *Eur J Endocrinol* 2004;151:657–87.



Speakers and Chairmen: Claus Gravholt, Lars Sävendahl, Ron Rosenfeld, Paul Saenger and Andrew Zinn.

cases, although up to 30% have some spontaneous puberty. Female sex steroid replacement therapy (HRT) is given during adult years. The optimal age of start and dose of HRT have not been established. Fracture risk is elevated in TS but is potentially lessened by GH and estrogen therapies (Fig. 3). Also HRT may improve liver function. Otherwise long-term benefits and/or drawbacks from HRT have not been thoroughly evaluated. Since risks for cardiovascular and endocrinological disease are elevated in TS, continuing medical care and surveillance during adulthood are required.

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The participants met in small international groups to discuss critical questions in the diagnosis and therapy of Turner syndrome.

How to prevent late diagnosis of TS?

- Develop an inexpensive genetic screening test since early diagnosis of TS is valuable in order to provide early intervention
- Education of obstetricians, neonatologists, primary care providers (PCP) to recognize phenotypic features and auxologic criteria

How best to screen for TS?

- Monitor growth rate using annual plotting on growth chart
- Obtain karyotype in any girl with height <5th percentile (or -2 SD for target height),
- Educate PCP regarding significance of slow growth velocity and target subspecialists such as cardiologist, gynecologist, endocrine PCP
- The earlier the diagnosis of TS, the better the TS child fares.

How to use the genotype-phenotype relationship to optimize diagnosis and treatment?

- Ascertainment bias continues to haunt genotype/phenotype studies.
- Need prospective studies of genotypic – phenotypic correlation with clinical follow-up to avoid this pitfall.
- Gonadectomy is indicated if there is clear Y material (with centromere) by conventional cytogenetics.
- Currently the best approach is clinical: we will treat the things that happen.

Is it beneficial to start GH treatment in TS girls earlier than 2 yrs of age?

- GH should be started when height falls below the 5th centile in TS children who have declining GV.
- There is no reason to avoid early GH start, although it may not change adult height.
- Data are needed to determine whether GH prior to age 2 yrs will benefit metabolic aspects, anatomy, development of motor coordination, eustachian tube growth.

Will GH dosing based on serum IGF-I levels be beneficial....for safety? ...for efficacy?

- IGF-I should be measured at least annually in TS patients on GH therapy. IGFBP-3 is also recommended in order to calculate the ratio. A TS registry would be of value, with data entry continuing through childhood and adulthood. Research on IGF-I titration of GH dosing in TS is recommended.

How to manage the transition of TS girls from the pediatric to the adult clinic?

- The pediatric endocrinologist should find an adult colleague who can capably receive the transfer of care. This can be an internist, endocrinologist, or specialist in ENT, fertility or cardiology.
- It is also important to educate the woman, so she knows what care she needs to be obtaining as an adult with TS.

Should GH treatment be continued in TS girls until achievement of peak bone mass (around 20–25 yrs of age)?

- Longitudinal studies of bone mineral density are needed in TS girls and women.
- In the meantime, we need to be sure that TS women take their estrogen, and optimize calcium and vitamin D intake.
- HRT in post-menopausal TS women is no longer recommended, because studies have shown no advantage with HRT in normal women.
- Currently HRT is not indicated in TS women >50 yrs old

How to overcome hearing problems in TS girls and women?

- Hearing problems can be disabling for the TS adult, whether resulting from prior otitis media or sensori-neural changes.
- Early identification of hearing problems is beneficial.
- Study of early GH or estrogen therapy is required to identify whether these might reduce hearing problems.