GONADAL PATHOLOGY AND RESPONSE TO GROWTH HORMONE THERAPY IN 45,X/46,XY FEMALES

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Turner syndrome

- 1/2500 births
- Variety of karyotypes and phenotypes
  - 50% 45,X monosomy
  - 50% mosaic

Broad shield like chest with wide spaced nipples, pectus excavatum
Lymphoedema
Elbow- valgus deformity
Webbed neck, low hairline
Cardiac disease

Short stature
Hearing loss
Scoliosis/ kyphosis
Primary or early gonadal failure
Renal anomalies
Coeliac, thyroid disease
Turner syndrome mosaicism with Y material

- 45,X/46,XY karyotype with female phenotype is rare
  - <1/15,000 births
  - 6-10% of Turner syndrome
  - Female phenotype if low proportion Y material (SRY)
Two unanswered questions

• Does karyotype influence growth potential?
  – In Australia, 45,X/46,XY girls cannot receive growth hormone tx unless have had gonadectomy

• What is the cancer risk in these girls?
Short stature homeobox (SHOX)

- **SHOX gene located on both X and Y chromosomes**
  - More prone to deletions on Xp
  - Usually inherit 2 functional copies
  - Important for growth and bone development

- **SHOX deletion:**
  - 1/2000-5000 worldwide
  - 1/40-150 short stature individuals
  - Haploinsufficiency in Turner syndrome
SHOX deficiency vs Turner: - height and GH response

• 2013 study (Blum et al, 75 pts)
  – Mean ht TS lower than SHOX pre GH tx
  – Ht SD score gain from start of tx to final ht similar (1.32-1.34) with same dose of GH
    → Children with SHOX deficiency responded similarly to TS girls when treated with same GH dose

Blum WF et al. JCEM 2013; 98(8): E1383-1392.
Gonadoblastoma risk in 45,X/46,XY girls

- Varying risks reported but usually accepted as 10-15%
- Related to testis-specific protein on Y (TSPY) gene?
- Risk relates to phenotype?
  - Cools et al (2011) suggest:
    - > 50% risk if ambiguous genitalia at birth
    - 2-3% risk if female phenotype
      - Low incidence testicular tissue
    - 18% unable to identify gonads (? apoptosis)

Cools M et al. JCEM 2011; 96(7): E1171-1180.
What does the literature say re gonadoblastoma risk and female phenotype?

Table 2
Series of Patients with Peripheral Blood Karyotype 45,X/46,XY and Turner Syndrome Phenotype Who Underwent Gonadectomy and Tumor Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Patients with Gonadal Tumors, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravholt et al (2000)</td>
<td>7</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Mazzanti et al (2005)</td>
<td>10</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Brant et al (2006)</td>
<td>7</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Cools et al (2011)</td>
<td>23</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Present Study</td>
<td>8</td>
<td>4 (50)</td>
</tr>
</tbody>
</table>

* Dysgerminoma; remainder of gonadal tumors were gonadoblastomas.

Aims of study

• To evaluate growth hormone response in Turner girls (TS) and 45,X/46,XY females

• To explore gonadoblastoma risk in 45,X/46,XY females
Methods

- Ethics approval from SCHN Ethics Committee
- Audit of patient records and endocrine database over last 30 years
- Final height data using database or GHAC data
- Comparisons made between TS and 45,X/46,XY groups
  - Mann-Whitney U test
- Independent review of all histopathology
198 females aged ≤30 years with TS or mixed gonadal dysgenesis

- **51 Turner syndrome** (with final height available)
  - 45,X (n=26)
  - Mosaic without Y material (n=25)

- **19 45,X/46,XY females** (final height available in 10)
  - 45,X/46,XY karyotype with TS phenotype (n=17)
  - Other cytogenetic abnormalities (n=2)
    - isochromosome Yq
    - 45,XO/48,XYY +12
Presenting features

- All 45,X/46,XY patients assigned female gender of rearing
- Age at diagnosis from pre-natal to 13 years

<table>
<thead>
<tr>
<th>Presenting Feature</th>
<th>Number</th>
<th>Age at Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical genitalia</td>
<td>8</td>
<td>Birth-3yo</td>
</tr>
<tr>
<td>- Clitoromegaly (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Labial fusion (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Absent or small uterus (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short stature</td>
<td>8</td>
<td>3-13yo</td>
</tr>
<tr>
<td>Dysmorphic features of Turner syndrome</td>
<td>3</td>
<td>Birth-11yo</td>
</tr>
<tr>
<td>Incidental antenatal karyotype finding</td>
<td>3</td>
<td>Antenatal</td>
</tr>
</tbody>
</table>
## Baseline characteristics at GH commencement

<table>
<thead>
<tr>
<th></th>
<th>TOTAL GROUP N=198</th>
<th>TURNER SYNDROME N=50 (95% CI)</th>
<th>45,X/46,XY FEMALES N=10 (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>9.1 (7.2 to 8.1)</td>
<td>8.1 (7.1 to 9.1)</td>
<td>7.7 (4.9 to 10.4)</td>
<td>0.37</td>
</tr>
<tr>
<td>Height SD</td>
<td>-2.4 (-2.6 to -2.2)</td>
<td>-2.5 (-2.7 to -2.2)</td>
<td>-2.3 (-2.8 to -1.9)</td>
<td>0.82</td>
</tr>
<tr>
<td>Mid-parental height SD</td>
<td>-0.14 (-0.4 to 0.1)</td>
<td>0.0 (-0.2 to 0.2)</td>
<td>-0.7 (-1.2 to -0.1)</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>GH dose (mg/m2/week)</td>
<td>7.1 (6.6 to 7.6)</td>
<td>7.1 (6.5 to 7.7)</td>
<td>7.0 (5.2 to 8.7)</td>
<td>0.59</td>
</tr>
<tr>
<td>Duration of growth hormone (years)</td>
<td>6.9 (5.9 to 7.9)</td>
<td>6.8 (5.8 to 7.8)</td>
<td>8.2 (4.6 to 11.7)</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>TURNER SYNDROME</td>
<td>45,X/46,XY FEMALES</td>
<td>P value</td>
<td></td>
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<td>--------------------------------</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>N=50 (95% CI)</td>
<td>N=9 (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height SD at 12 months</td>
<td>-2.0 (-2.3 to -1.8)</td>
<td>-1.9 (-2.3 to -1.5)</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Change in height SD at 12 months</td>
<td>0.4 (0.3 to 0.5)</td>
<td>0.4 (0.2 to 0.7)</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Final height SD</td>
<td>-1.6 (-1.8 to -1.4)</td>
<td>-0.8 (-1.4 to -0.1)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Final height SD minus initial height SD</td>
<td>0.9 (0.7 to 1.0)</td>
<td>1.5 (1.1 to 2.0)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Final height SD minus MPH SD</td>
<td>-1.6 (-1.8 to -1.4)</td>
<td>-0.3 (-1.3 to 0.7)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>
Comparison of final height SD

Turner vs 45,X/46,XY Females

Comparison of final minus initial height SD

Turner vs 45,X/46,XY Females

Comparison to target height SD

Turner vs 45,X/46,XY Females
Percentage of Y material on karyotype is not associated with MPH or final height SD.
Conclusions re growth

• 45,X/46,XY females respond better to growth hormone treatment over time than Turner girls
Study population for gonadal pathology analysis

- Across SCHN
- **19 45,X/46,XY females aged ≤30 years**
  - 45,X/46,XY karyotype with TS phenotype (n=17)
  - Other cytogenetic abnormalities (n=2)
    » isochromosome Yq
    » 45,XO/48,XYY +12
Gonadal differentiation in 45,X/46,XY girls (SCHN)

45,X/46,XY females (19 pts, 38 gonads)

Atypical genitalia at birth (n=8 patients, 42%)

- 8 pts (16 gonads)
  - gonadectomy (at 1-34mo)
    - 1/16 normal ovary
    - 3/16 streak gonads
    - 3/16 streak ovaries
    - 5/16 ovotestis
    - 4/16 testes
    - Y material 16-70%

Female phenotype at birth (n=11 patients, 58%)

- 11 pts (22 gonads)
  - gonadectomy (at 1mo-14yo)
    - 4/22 streak gonads
    - 16/22 streak ovaries
    - 2/22 ovotestis
    - Y material 12-100%

Genitalia appearance at birth is significantly associated with presence of testicular parenchyma ($\chi^2 = 10.0, p<0.01$)
Gonadoblastoma risk in 45,X/46,XY girls (SCHN)

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- 1/16 ovary
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- 4/16 testes

Female phenotype at birth (n=11 patients, 22 gonads)
- 4/22 streak gonads
- 16/22 streak ovaries
- 2/22 ovotestis

3/16 gonads (18.8%) gonadoblastoma (2 definite, 1 equivocal)

11/22 gonads (50%) gonadoblastoma

No significant association between genitalia appearance and gonadoblastoma risk ($\chi^2 = 3.9$, p=0.05)

No significant association between presence of testicular parenchyma and gonadoblastoma risk ($\chi^2 = 0.6$, p=0.4)

1/3 gonads also Stage 1 dysgerminoma (2mo)

3/9 gonads also Stage 1 dysgerminoma (11 and 13yo)
Gonadoblastoma risk in 45,X/46,XY girls

**Gonadoblastoma risk in 45,X/46,XY girls (SCHN)**

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**Female phenotype at birth**
- (n=11 patients, 58%)
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  - 16/22 streak ovaries
  - 2/22 ovotestis
  - 11/22 gonads (50%) gonadoblastoma
  - 3/9 gonads also Stage 1 dysgerminoma (11 and 13yo)

**cf. Cools 2011 study**
- 52% risk
- 2.2% risk
- Mean age gonadectomy 0.6yrs
- Mean age gonadectomy 7.3 yrs
- cf. Cools 2011 2.2 yo
Conclusions

• Phenotype at birth or gonadal differentiation pattern is not associated with risk of gonadoblastoma

• Difficult to predict risk of gonadoblastoma in females with 45,X/46,XY karyotype
  – Recommendation for early gonadectomy in all girls
Future work

• Australia and NZ wide study looking at gonadal pathology in 45,X/46,XY females is currently underway
Acknowledgements

- Multidisciplinary teams involved in patients’ care
- Dr Grahame Smith, Dr Kim Matthews
  - Urology and Gynaecology
- Dr Nicky Graf
  - Histopathology
- CHW Radiology, Histopathology Medical Records
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