Endocrine Issues in Trisomy 21

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Conflict of Interest

- None to declare
Objectives

• To understand the prevalence of thyroid abnormalities in T21
• To review the current recommendations for thyroid screening and management
• To review other hormone problems that can present in children with T21
Trisomy 21

- Down syndrome is the most common chromosomal abnormality
- Almost 10,000 children are born with Down syndrome in the United States each year (one in 691 live births; prevalence of 10.3 per 10,000)
- Birth rates are highest among mothers of advanced maternal age however 80% of all children with Down syndrome are born to mothers younger than 35 years
- The underlying karyotype is 95% non-familial trisomy 21 (47 total chromosomes), 3% to 4% unbalanced translocation, and 1% to 2% genetic mosaicism
- Despite an increased risk of chronic disease, life expectancy for individuals with DS has continued to improve with an estimated mean survival approaching 60 years of age
Overview

• Thyroid abnormalities in T21
  • Hypothyroidism
  • Hyperthyroidism
• Growth
  • Short stature
• Obesity
• Autoimmune disease
  • Diabetes
    • Type 1
    • (Type 2)
  • Coeliac disease
• Puberty and fertility
THYROID PROBLEMS IN T21
The Thyroid Gland
Thyroid Histology

Thyroid Gland
H&E

lobule

follciles

interlobular connective tissue
Thyroid Hormone Synthesis

Thyroid Follicular Epithelial Cell

Iodine Active Transport

T4/T3 release into circulation

T4

Processed Thyroglobulin Lysosomal Degradation and release of T4, T3, MIT, and DIT

Oxidation and organification of Iodine by performed by Thyroid Peroxidase

MIT

DIT

Coupling of MIT and DIT by Thyroid Peroxidase

Processed Thyroglobulin Endocytosis
Control of Thyroid Hormone production

Hypothalamus

TRH

Anterior Pituitary

TSH

Thyroid Gland

T4, T3

Target Tissues

Iodinase

T4, T3, rT3

T3

Major Regulatory Step
TSH Release

Negative Feedback Control
Functions of thyroid hormone

**Metabolism**
- Enhances whole-body metabolism: increased basal metabolic rate and body temperature

**Autonomic Nervous System**
- Enhance sympathetic nervous system activity: increasing heart rate and cardiac output

**Normal Linear Growth**
- Together with GH: enable normal linear growth to adult stature

**CNS**
- Potentiate brain development in fetuses and neonates
- In adults, thyroid hormones appear to speed up the brain's activity

**GI System**
- Enhance GI motility: hypothyroidism can result in constipation while hyperthyroidism yields hyperdefecation
Thyroid Disorders in T21

- Congenital hypothyroidism
  - Mostly due to thyroid hypoplasia
- Subclinical hypothyroidism
- Acquired Hypothyroidism
  - Autoimmune hypothyroidism
  - Non-autoimmune (TPO antibody negative)
- Hyperthyroidism
  - Graves disease
Thyroid Function Tests

Major Regulatory Step
TSH Release

TPO antibodies

TSH Receptor antibodies
## TFTs

<table>
<thead>
<tr>
<th>Test</th>
<th>Hypothyroidism</th>
<th>Subclinical Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (0.3-5.0) mU/L</td>
<td>↑</td>
<td>↑ (&lt;10)</td>
<td>↓</td>
</tr>
<tr>
<td>Free T4 (10-20) pmol/L</td>
<td>↓</td>
<td>Normal</td>
<td>↑</td>
</tr>
<tr>
<td>Free T3 (3.5-6.5) pmol/L</td>
<td>(↓)</td>
<td>(Normal)</td>
<td>↑</td>
</tr>
<tr>
<td>Thyroid Antibodies</td>
<td>TPO antibodies</td>
<td></td>
<td>TSH Receptor antibodies</td>
</tr>
</tbody>
</table>
Congenital Hypothyroidism

• 28-fold increase in DS (1 in 140)
• Not generally due to usual causes (aplasia or ectopia)
  • ? Hypoplasia
  • ? abnormal hypothalamic–pituitary–thyroid feedback
• Mild abnormalities at birth increase with time
• Should be picked up on newborn screen
Acquired Hypothyroidism

- ~⅓ of DS kids will develop by age 25
- Non-autoimmune hypothyroidism (~50%)
  - thyroperoxidase antibodies negative
  - ? milder form of congenital hypothyroidism
- Autoimmune hypothyroidism (~50%)
  - associated with thyroperoxidase antibodies
  - generally occurs after age 8
- Symptoms
  - poor growth, dry skin, constipation, lethargy, weight gain
  - goitre uncommon
  - difficult to differentiate in kids with DS
Subclinical Hypothyroidism

• 7-40% of young people with DS
• Definition:
  • elevated TSH (usually <10) with normal Free T4
  • Usually asymptomatic
  • May resolve by 4-5yrs of age; those with goitre have lower rates of remission
  • <50% progress to overt hypothyroidism

Kariyawasam, Hormone Research, 2014
# Subclinical Hypothyroidism

## Table 2
Comparison of findings regarding clinical sequelae of mild hypothyroidism in DS

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Definition</th>
<th>Clinical Sequelae of Mild Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharav and Collins(^{30})</td>
<td>94</td>
<td>TSH &gt;5.7 mU/L</td>
<td>Decreased linear growth, weight gain, and head growth</td>
</tr>
<tr>
<td>Selikowitz(^{31})</td>
<td>101</td>
<td>TSH &gt;3.8 (units not given)</td>
<td>No effect of isolated increases of TSH on growth or intelligence. 40% had spontaneous resolution of increased TSH</td>
</tr>
<tr>
<td>Tirosh et al(^{33})</td>
<td>44</td>
<td>N/A</td>
<td>No improvement in cognitive, social, or physical attributes after 8–14 wk of thyroid hormone replacement for low-borderline thyroid functions</td>
</tr>
</tbody>
</table>

Van Trotsenburg et al, JCEM, 2005  
Marchal, JCEM, 2014  
Grabber et al, 2012
Hypothyroidism – Treatment

- L-thyroxine (Synthroid) to normalize TSH

- ? recommendation for treatment in subclinical hypothyroidism
Hyperthyroidism

• Occurs in ~2% of kids with DS by age 25
• Autoimmune (Graves disease)
• Associated with TSH-receptor antibodies
• Symptoms: hyperactivity, inattention, weight loss, increased appetite
• May have goitre
• Treatment:
  • anti-thyroid medication (methimazole/Tapazole)
  • radioiodine ablation
  • surgery
Screening for Thyroid Problems

• Recommendation: check TSH at birth, 6 and 12 months, and then annually
  • This interval is controversial; UK recommendations suggest 5yrly testing

• Check free T4 as well if clinically suspicious, or if TSH abnormal
  • Thyroperoxidase (TPO) antibodies

AAP Recommendations, 2011
Case 1

• Tommy is a 4-year-old boy who is followed annually by his pediatrician
• His TSH has been 3.8, 4.7, 5.6 and now 6.4 mU/L over the past 2 years (normal 0.5–5.0 mU/L)
• He appears normal

• What further tests would you do?
• Would you treat him?
• Would the answers change if he were 12yo?
Case 2

• 4yo girl with T21
• Routine thyroid screen
• TSH <0.01 (normal 0.5–5.0 mU/L)

• What next?
• What symptoms would you look for?
• How would you treat her?
GROWTH IN DOWN SYNDROME
Height and Weight

- DS is most common chromosomal cause of short stature
- 500 g below average at birth
- 2–3 cm below average at birth
- Growth failure continues post-natally
- Poor, delayed pubertal growth spurt
- Growth hormone is NOT indicated
New Growth Charts (Finally!)

- DSGS (Down Syndrome Growing Up Study)
- Convenience sample of children with DS up to 20yrs – followed longitudinally
- Sex-specific growth charts developed for birth to 36mo and 2-20yrs using LMS method
- Developed using 1520 measurements on 637 participants
- Growth pattern is similar to a modern UK cohort (Styles and Cole et al, ADC, 2002)
- Overall, weight gain in children <36mo and stature for males are improved compared with older growth charts.

Zemel et al, Pediatrics, Nov 2015
**FIGURE 1**

Curve comparisons for weight in kilograms and length in centimeters for male and female subjects, birth to 36 months of age. Contemporary curves from the DSGS (solid line) are compared with those from the US 1988 curves from Cronk et al (dotted line) and the UK 2002 curves from Styles et al (dashed line).
FIGURE 2
Curve comparisons for weight in kilograms and height in centimeters for male and female subjects, 2 to 20 years of age. Contemporary curves from the DSGS (solid line) are compared with those from the US 1988 curves from Cronk et al (dotted line) and the UK 2002 curves from Styles et al (dashed line).
Weight Charts – 2-20 yrs

Zemel et al, Pediatrics, Nov 2015
Height Charts – 2-20 yrs

Zemel et al, Pediatrics, Nov 2015
Obesity in T21

- Prevention of obesity is an important goal
- DS have reduced resting metabolic rate
- Infants usually light for height
- Progress to being proportional
- By 3-4yo, they are more likely than not to be obese
Strategies for Obesity Prevention

- Lifelong monitoring of growth
- Aim to prevent obesity from 24mths
- Food selections
  - Diet should aim for nutrient rich, high fibre foods
  - Total calorie intake should be <RDA
  - Consider supplementary vitamins/minerals
  - Consider calcium intake and vit D
- Behavioural interventions
  - Physical activity
  - Social activity
AUTOIMMUNE DISEASE
Diabetes

- **type 1: autoimmune**
  - up to 2% of kids with DS (20-fold increase)
  - often associated with thyroid and celiac
  - managed with insulin, meal plan
- **type 2: insulin resistance**
  - incidence rises with age, body-mass index
  - more common in females, family history
  - initially managed with oral medication
Signs/Symptoms of Diabetes

Know the Diabetes Warning Signs!

- Urinating a lot
- Losing weight
- Lacking energy
- Drinking a lot

If your child shows these signs, seek immediate medical attention.

Diabetes can affect children at any age. If left untreated, diabetes is deadly.
Coeliac Disease

- An immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals
- Increased prevalence in DS
  - 4.6%-13% of children with DS have CD
- Presentation:
  - 44-69% of children with DS have abdominal complaints symptomatic of CD at diagnosis
  - 11-39% have signs of the disease: growth failure, anemia
  - 17-50% are asymptomatic at diagnosis

Swigonski et al, Pediatrics, 2006
Coeliac Disease

• Universal screening not recommended for asymptomatic individuals

• Test using tTG (+ IgA)

• Consider HLA typing if available (specifically HLADQ2 and DQ8)

Symptom Review

• Diarrhoea
• Constipation
• Slow growth
• Unexplained failure to thrive
• Anaemia
• Abdominal pain or bloating
• Refractory developmental or behavioural problems

AAP Recommendations, 2011
ESPGHAN Guidelines, 2012
PUBERTY AND FERTILITY
Puberty and Fertility – Girls

- Generally, normal tempo and sequence of physical, emotional changes; onset may be slightly delayed
- Pubertal growth spurt less robust in DS
- Weight gain more preserved, leading to obesity
- Menstrual cycles are usually regular
- Menstrual hygiene
- Usually fertile
  - risk of T21 for offspring depends on maternal karyotype
- ? some evidence of early gonadal failure
- Risk of osteoporosis ?related to hypogonadism

Angelopoulou, Int J Gyne & Obs, 1999
Puberty and Fertility – Boys

- Onset of puberty may be a bit delayed, particularly in boys with DS
- Pubertal growth spurt less robust in DS
- Weight gain more preserved, leading to obesity
- Cryptorchidism, small testes, oligospermia, micropenis and ambiguous genitalia have been described
- ↑ infertility, testicular failure and malignancy

Sakadamis et al, 2000
Questions