Endocrine Issues in Trisomy 21

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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
Overview

- Thyroid abnormalities in T21
  - Hypothyroidism
  - Hyperthyroidism
- Growth
  - short stature
- Obesity
- Autoimmune disease
  - Diabetes
    - Type 1
    - (Type 2)
  - Coeliac disease
- Puberty and fertility
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
The Thyroid Gland
Thyroid Histology

Thyroid Gland
H&E

lobule
follicles
interlobular connective tissue
Structure of Thyroid Hormones

Triiodothyronine (T3)

Thyroxine (T4)

L-tyrosine
Thyroid Hormone Synthesis

Iodine Active Transport

Iodine salvage from MIT and DIT

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

Oxidation and organification of Iodine by performed by Thyroid Peroxidase

Coupling of MIT and DIT by Thyroid Peroxidase

Processed Thyroglobulin Endocytosis

T4/T3 release into circulation
Deiodinases

DIOI: Liver, Kidney, Thyroid

DIOII: Pituitary, Brain, Placenta, BAT

DIOIII: Fetal tissues, Placenta
Thyroid Hormone Transport

- T4 and T3 are highly hydrophobic therefore are largely protein bound in the circulation (99.9% T4 and 99.7% T3)
- Thyroxine Binding Globulin (TBG)
  - The major binding globulin (around 80% of bound T4)
  - Affinity T4>>T3
- Transthyrethrin (TTR)
- Albumin
Control of Thyroid Hormone production

Major Regulatory Step
TSH Release

Hypothalamus
TRH

Anterior Pituitary
TSH

Thyroid Gland
T4, T3

Target Tissues
Iodinase
T4, T3, rT3

T3

Negative Feedback Control
Functions of thyroid hormone

- Increases cardiac output
- Increases heart rate
- Increases ventilation rate
- Increases basal metabolic rate
- Potentiates the effects of catecholamines (i.e. increases sympathetic activity)
- Potentiates brain development
- Thickens endometrium in females
- Increase metabolism of proteins and carbohydrates (i.e. they have a catabolic action)
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

<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)
- Should be picked up on newborn screen
  - Heal prick test at 48-72hrs of age in all babies
  - Measures TSH
- Not generally due to usual causes (aplasia or ectopia)
  - ? Hypoplasia
  - ? abnormal hypothalamic–pituitary–thyroid feedback
- DS have shifted ‘normal range’ for TSH and free T4
  - ? significance
- Mild abnormalities at birth may increase with time
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
- Independent of prematurity, LBW, prolonged delivery
- Usually asymptomatic
- May resolve by 4-5yrs of age; those with goitre have lower rates of remission
  - <50% progress to overt hypothyroidism

- DS have shifted ‘normal range’ for TSH and free T4
  - ? significance

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>

Graber et al, 2012
Hypothyroidism – Treatment

• L-thyroxine (Synthroid) to normalize TSH

• Treatment of subclinical hypothyroidism is controversial

Why treat?
• Development
  • Mild motor delay at 24 mths in children treated with placebo v T4
  • Not persistent at 10 years
• Improved growth

Van Trotsenburg et al, JCEM, 2005
Marchal, JCEM, 2014
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)
  - radiiodine ablation
  - surgery
Screening for Thyroid Problems

- DS is associated with a wide variety of abnormalities of thyroid function and hormone levels
- 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
## Screening for Hypothyroidism

### Table 1

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Definition</th>
<th>% With Mild Hypothyroidism</th>
<th>% Spontaneous Resolution of Mild Hypothyroidism</th>
<th>Screening Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bull et al (AAP guideline)³</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>TSH screen at 6 and 12 mo of age, then annually thereafter</td>
</tr>
<tr>
<td>Cutler et al¹¹</td>
<td>44</td>
<td>6.6–26.8 microunits/mL</td>
<td>27</td>
<td>80</td>
<td>Routine screening (duration between testing not discussed)</td>
</tr>
<tr>
<td>Gibson et al¹⁹</td>
<td>103</td>
<td>≥6 mU/mL</td>
<td>N/A</td>
<td>70</td>
<td>Thyroid screen every 5 y for patients with initial testing revealing isolated increase of TSH unless symptoms develop</td>
</tr>
<tr>
<td>Tuysuz and Beker²⁶</td>
<td>320</td>
<td>6–20 mU/L (compensated hypothyroidism)</td>
<td>25</td>
<td>N/A</td>
<td>Thyroid screen annually for patients with normal thyroid functions. Screening every 3 mo for those with compensated hypothyroidism</td>
</tr>
</tbody>
</table>

Graber et al, 2012
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?
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

- [www.growthcharts.com](http://www.growthcharts.com)
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
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 weight loss +/- oral medication
Signs/Symptoms of Diabetes

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

• Symptom Review:
  • Diarrhoea
  • Constipation
  • Slow growth
  • Unexplained failure to thrive
  • Anaemia
  • Abdominal pain or bloating
  • Refractory developmental or behavioural problems
• Universal screening not recommended for asymptomatic individuals
• Test using tTG (+ IgA)

AAP Recommendations, 2011
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
  - Sexual education is important +/- birth control
- Early menopause
- 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
- Risk of osteoporosis ?related to hypogonadism

Sakadamis et al, 2000