Congenital hypothyroidism (CH): management of mild cases

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Disclosure

Guy Van Vliet has reported no commercial affiliation associated with this presentation
Learning objectives

At the conclusion of this presentation, the participant should be able to:

1. Differentiate screening for and diagnosis of CH
2. Make a differential diagnosis of neonatal hyperthyrotropinemia
3. Counsel parents about the causes and consequences of overt and mild CH
Biochemical screening for CH: rationale

Severe CH, 4 mo:
- easy diagnosis
- too late for brain

Which of these twins, aged 14 d, has severe CH?

Of ~ 300 newborns sent by the screening lab, only 2 suspected clinically.

TSH 2.12
fT4 19.6

TSH 109
fT4 6.5
99mTc scintigraphy establishes etiology of overt CH in 20 min., within 24 hours of screening result, before 2 weeks of age

**Ectopy***: 70% missed by ultrasound
(Jones et al, Pediatr Radiol 40: 725, 2010)

**Athyreosis**: 15%
-true (Tg undetectable)
-apparent (Tg measurable)*

**Dyshormonogenesis***: 10-15%
Goiter, ↑ uptake, N shape/site)
(missed clinically in ~ 90%)
(25% recurrence risk in sibs)

* May have only mild ↑ in TSH
Screening for a disease generally increases prevalence estimates: CH is no exception

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
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<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>~ 1 in 6,500*</td>
<td>~ 1 in 2,500**</td>
</tr>
</tbody>
</table>

* Alm et al, BMJ 289:1171, 1984
**Deladoëy et al, JCEM 96: 2422, 2011

Even since screening, many laboratories report a steadily increasing incidence
Increase in positive CH screening tests

New York state

Harris and Pass, Mol Gen Met 91: 268, 2007

2-day CDC conference (Pediatrics, 5/2010)
TSH cut-offs in Lombardy

<table>
<thead>
<tr>
<th>Cut-off (mU/L)</th>
<th>Prevalence</th>
<th>On Rx (%)</th>
<th>in situ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1:2,654</td>
<td>85</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>1:1,154</td>
<td>43</td>
<td>68</td>
</tr>
</tbody>
</table>

(Corbetta et al, Clin Endo 71: 739, 2009)
### TSH cut-offs in Greece

<table>
<thead>
<tr>
<th>Cut-off (mU/L)</th>
<th>Recall rate (%)</th>
<th>Confirmed permanent</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.12</td>
<td>1:3,300</td>
</tr>
<tr>
<td>10</td>
<td>1.2</td>
<td>1:1,749</td>
</tr>
</tbody>
</table>

The ‘price’ of a two-fold increase in detection is a 10-fold increase in recall rate

(Mengreli et al, JCEM 95: 4283, 2010)
Québec: time trends by etiology

Global \uparrow\ in prevalence accounted for by:
- \downarrow\ in TSH cut-off (15\rightarrow5) on 2\textsuperscript{nd} sample
- CH w/thyroid \textit{in situ} or unknown cause

(Deladoëv \textit{et al.}, JCEM 96: 2422, 2011)
Mild ↑ TSH at screening: Pt 1

- 2\textsuperscript{nd} child (girl) of healthy, unrelated parents
- Brother, 2 y, neonatal TSH normal
- Pregnancy: IUGR noted, hence labor induced
- Born 38 w, C/S re: fetal distress, wt 1,670 g
- Transient hypoglycemia and RDS
- Screening day 2: TSH 28  total T\textsubscript{4} 45
- Serum day 12:  TSH 27  fT\textsubscript{4} 10.4
- Mother: TSH 0.5, TPO antibodies negative
$^{99mTc}$ scintigraphy:

- Normal shape, size and location
- Very low uptake
Patient 1 (continued)

- **Rx:** $L-T_4$ 25 $\rightarrow$ 50 µg/d. because of $\uparrow$ in TSH
- Diagnosis of craniosynostosis (Crouzon-type)
- Unspecified dysmorphic syndrome
- Sitting at 11 months, mild speech delay
Clinical photographs at age 2 y 9 months
Patient 1 (continued)

- Age 3 y, Rx stopped: TSH 55, fT<sub>4</sub> 5.5
- Age 7 y, stocky, small hands and feet:
  - Ca: 2.51
  - PTH: 29
- **GNAS** analysis: c.344C>T (p.P115L)
Patient 2

Mom’s BMI: 24.5
Dad’s BMI: 30.1

PubMed search: 'PHP & craniosynostosis':

**PHP Type 1a Caused by GNAS Mutation (deltaN377), Craniosynostosis, and Severe Trauma-Induced Bleeding.**


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<table>
<thead>
<tr>
<th>Mother's Stature</th>
<th>Father's Stature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*To Calculate BMI: Weight (kg) = Stature (cm) x Stature (cm) x 10,000 or Weight (lb) = Stature (in) x Stature (in) / 703
Mild ↑ TSH at screening: Pt 2
(Lucas-Herald et al, JPEM 26: 583, 2013)

- Boy born at 41 w, forceps, BW 3,430 kg
- Two older sisters in good health
- Referred at 11 days re: spot TSH 11
- Day 5 (Mom’s history): TSH 27, fT₄ 26
- Day 11 (on referral): TSH 13, fT₄ 20
- Decision to observe without treatment
- Strong family history noted (M, F, aunt)
Pt 2: ped. endo. evaluation

• Day 57:
  – Neither dysmorphism nor sign of hypo
  – Serum: TSH 21, fT₄ 15, Tg 63 µg/L
  – Echo: heterogeneous, ‘slightly small’
  – $^{99m}$Tc: no uptake (‘apparent athyreosis’)
  – Abs to TPO & TSHR (mom+baby): negative

• Day 94:
  – Serum: TSH 13, fT₄ 18, Tg 64 µg/L
  – Echo: homogeneous, volume low normal
Patient 2: follow-up

- Treatment from day 94 (25 → 50 µg/d)
- 6 TFTs/3 y: median TSH 5.3, fT₄ 18
- Novel missense heterozyg. mut. in TSHR (c.1196G>T; p.C390F) in child & mother
- Also in euthyroid mat. GM (TSH 1.8)
- Not in father (TPO Abs+), nor in sister
- \textit{GNAS} sequence normal in proband
Patient 2: further follow-up

- Rx stopped in proband and mother
- **Proband:**
  - 6 weeks after stopping: TSH 14.6, fT\(_4\) 13
  - 6 months after stopping: TSH 8.5, fT\(_4\) 16.7
- **Mother:**
  - Off treatment, TSH 6.4 and fT\(_4\) 13
  - Fatigue → Rx re-started by G.P. after 6 w
Mild ↑ TSH at screening: Pt 3

- Girl, 1st child, healthy, unrelated parents
- Born at 41 w after induced labor
- BW 3,460 g, APGAR 91, 105
- Day 1: RDS, pulmonary hypertension
- Day 2: screening TSH 31, total T4 245
- Day 12: serum TSH 17, fT4 12
- De novo, novel, het. NKX2.1 mut. (I207F)
  (DNA binding & transactivation of Tg & SP-B, Maquet et al, JCEM 94:197, 2009)
Pt 3: Brain-Lung-Thyroid syndrome

In spite of mechanical ventilation, L-T\textsubscript{4}, surfactant, pulm. vasodilators, death Day 40

Day 1

Day 39

Lungs: low alveolar counts, impaired branching

HPS 25x

Masson trichrome 100x

Couple has had a healthy child since then
Screening: begins a process...

协调发展导致诊断一系列条件:

- Overt CH (dysgenesis/dyshormonogenesis)
- Hyperthyrotropinemia: isolated/syndromic

因此至关重要的是:

- 建立病史 (99mTc 扫描: 肾上腺切除术)
- 记录结果/重新评估是否需要治疗
Treating patients, not numbers

○ Once ectopy has been ruled out:
  • Cause of ↑ TSH? Transient or permanent?
  • How many have mutations in GNAS, TSHR, NKX2.1 or 2.5, PAX8, THR, TSHB?
  • Most cost-effective approach: targeted exome sequencing + MLPA?

○ Risk of intellectual disability?

○ Impact of L-T4 treatment on outcome?
Strategies to assess risk of ↑ TSH for ↓ IQ

Compare areas with cut-off of 6 & 10

TSH distribution at screening (Québec, 2012)

Randomize newborns w/TSH 10-15 mU/L to L-T₄ or placebo
38% of children labeled as having CH (1 in 2,300) in the USA are no longer treated after age 4 y (Kemper et al, BMC Pediatrics, 2010)
Should we worry about transient neonatal hyperthyrotropinemia?

<table>
<thead>
<tr>
<th>Patient</th>
<th>Neonatal TSH</th>
<th>IQ at 5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;100</td>
<td>112</td>
</tr>
<tr>
<td>2</td>
<td>&gt;100</td>
<td>103</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>109</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>106</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>114</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>98</td>
</tr>
<tr>
<td>Patients</td>
<td>Mean±SD</td>
<td>107±6</td>
</tr>
<tr>
<td>Controls</td>
<td>Mean±SD</td>
<td>103±11</td>
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Transient neonatal hyperthyrotropinemia (even when severe) does not seem harmful (Alm et al, BMJ 289:1171-5, 1984)

PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Guy Van Vliet)
Newborn screening: gaps in the evidence

The harms likely from newborn screening largely relate to the worry caused by false positive results or, worse, results of uncertain significance—which leave parents in limbo, uncertain whether or not their child is affected—and to overmedicalization in cases where treatment is not needed, with attendant anxiety and costs of unnecessary clinical care. These are not trivial issues and are sure to increase if, in the near future, newborns are screened by whole-genome, exome, or more targeted genetic sequencing.

(Wilcken, Science 342:197, 2013)
Don’t get me wrong: screening for CH is a public health triumph!

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<td><strong>Mean IQ</strong></td>
<td>~ 86</td>
<td>~ 105</td>
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<tr>
<td><strong>% with IQ &lt; 70</strong></td>
<td>8 to 27 %</td>
<td>None</td>
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...but there is no need to make it too sensitive!

...and it is essential to document outcome

Thanks to...

• Ste-Justine:
  – Endocrinology: staff, fellows & lab
  – Genetics: J. Maassen et al
  – Clin. mol. biol. lab: I. Thiffault et al
• Screening lab: Y. Giguère et al
• M.D.s ‘feeding’ the Québec database
• ...you for your attention
• ... and visit http:www.thyroid4kids.org