Challenges in congenital hypothyroidism: understanding molecular pathophysiology and optimizing outcome

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Belgian Thyroid Club
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What I am not going to talk about:

- Maternal hypothyroxinemia
- Hypothyroxinemia of prematurity
- Thyroid dysfunction in Down syndrome
Pituitary:

\[ \beta TSH \]

Hypothalamus: TRH

\[ TRHR \]

Pituitary: \( \beta TSH \)

\[ TRHR \]

Iodine

Thyroid: PDS, THOX2, TPO, Tg, DEHAL

\[ NIS \]

\[ TSHR \]

\[ T_4 \]

\[ MCT8 \]

\[ DIO1, DIO2 \]

\[ T_3 \]

\[ T_3R \]

Negative feedback loops

Differentiation/Survival of lingual thyroid: PAX8, TTF1, TTF2

Migration:

TTF2? Extrinsic?

Development: Brain

Growth: Skeleton

Metabolism
Embryology of the thyroid: median anlage

• Before 8 weeks:
  - migration: tongue → neck
  - shape: round → bilobed

• By 10 weeks:
  - Thyroid follicular cells can be identified
  - Iodine concentration/iodothyronine synthesis

• Until 18-20 weeks:
  hypothalamo-pituitary control is quiescent
  (TSH plays no role in migration)
The thyroid of the 32-d human embryo already has lateral expansions

Thyroglossal tract

(O’Rahilly and Müller, Developmental stages in human embryos, 1987)
Embryology of the thyroid: lateral anlage

- Ultimobranchial body
- Derives from the fourth pharyngeal pouch
- Origin of:
  - Calcitonin-producing parafollicular cells (C-cells)
  - Some follicular cells, as shown by:
    - lateral Tg-positive structures in cases of lingual thyroid
      (Williams et al, J Pathol 159:135, 1989)
    - when only thyroid tissue is a “lateral thyroid ectopy“
      (Kumar et al, Thyroid: 10:363, 2000)
In cases of lingual thyroid, the thyroid arteries are hypoplastic (Cir. Urug. 55: 286, 1985; AJNR 11: 730, 1990; J Belge Radiol 76:241, 1993)

Cause or consequence of the regression of the lateral expansions? Could explain why calcitonin is low (Chanoine et al, J Endocrinol Inv 13:97, 1990)
Proliferating thyroid precursors cells extend laterally along a course that coincides with that of a paired vessel subdivision of the former aortic sac

*indicates thyroid-vessel interface in the midline

PAA3 = 3\textsuperscript{d} pharyngeal arch artery

Thyroid bilobation is guided and possibly also induced by transient embryonic vessels

*(Fagman et al, Developmental Dynamics, 235:444, 2006)*
Permanent Primary Congenital Hypothyroidism (CH): a window into thyroid gland development

- Incidence: ~ 1/3500 newborns in iodine-sufficient areas
- Most common preventable cause of mental retardation
- Thyroid dysgenesis: isolated malformation with a female predominance and a sporadic occurrence, comprises:
  - ectopy (most often sublingual) (~ 70 %)
  - thyroid agenesis or athyreosis (~ 15 %)
  - orthotopic hypoplasia, hemiagenesis (< 5%)
- Thyroid dyshormonogenesis: (~ 10-15 %)
  - autosomal recessive
  - leads to goiter
Newborn with ectopic (sublingual) tissue

Newborn with athyreosis (confirmed by undetectable plasma thyroglobulin)

Newborn with a large goiter (normal position and shape) (dyshormonogenesis)

Frontal views  Lateral views
Echo cannot replace scintigraphy

<table>
<thead>
<tr>
<th>Echo</th>
<th>No uptake</th>
<th>Ectopic</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No tissue</td>
<td>3</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Ectopic</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Normal</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased volume</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hypoplasia</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Perry et al, Hormone Res 58 (suppl 2): 64, 2002)
Thyroid dysgenesis: isolated or associated?

• Prevalence of congenital heart malformations, mostly septation defects: increased 4- to 7-fold (Devos et al, JCEM 84: 2502, 1999; Castanet et al, JCEM 86: 2009, 2001; Olivieri et al, JCEM 87: 557, 2002)

• Similar molecular mechanisms involved in thyroid differentiation/migration/growth and in septation of the embryonic heart (5-7 weeks)?

• NKX2.5 mutations? (JCEM 91:1428-33, 2006)
### Thyroid dysgenesis: proportion of girls

<table>
<thead>
<tr>
<th>Reference</th>
<th>Yr</th>
<th>Nb</th>
<th>Athyreoses</th>
<th>Ectopies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verelst, 91</td>
<td>74-88</td>
<td>61</td>
<td>0.63</td>
<td>0.79</td>
</tr>
<tr>
<td>Devos, 99</td>
<td>88-97</td>
<td>177</td>
<td>0.58</td>
<td>0.74</td>
</tr>
<tr>
<td>Fisher, 00</td>
<td>80-96</td>
<td>35</td>
<td>0.47</td>
<td>0.75</td>
</tr>
<tr>
<td>Hanukoglu, 01</td>
<td>85-95</td>
<td>85</td>
<td>0.61</td>
<td>0.78</td>
</tr>
<tr>
<td>Connelly, 01</td>
<td>77-97</td>
<td>234</td>
<td>0.61</td>
<td>0.73</td>
</tr>
<tr>
<td>Lobo, 03</td>
<td>92-02</td>
<td>134</td>
<td>0.67</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Sex ratio not compatible with dominant or recessive inheritance, especially in ectopy.
Sexual dimorphism in biochemical severity of congenital hypothyroidism

• Ectopy: girls more severely affected
• Athyreosis: boys more severely affected
• Dyshormonogenesis: no sex difference

→ Quantity and functional capacity of ectopic tissue should be estimated and compared between sexes
→ Further evidence that ectopy and athyreosis are different entities at the time of birth
→ Sexual dimorphism should be considered in studies of the molecular mechanisms of thyroid dysgenesis

(Eugène et al, JCEM 90:2696-2700, 2005)
The Mendelian line of thought

- Affected relatives in 2% of cases of CH from thyroid dysgenesis (Castanet et al, JCEM 86:2009, 2001)
- By ultrasound, 8% of asymptomatic thyroid developmental abnormalities (mostly thyroglossal tract remnants) in euthyroid 1st degree relatives of children with CH from dysgenesis vs 0.8% in controls (Léger et al, JCEM 87: 575, 2002)
- Proposed mechanisms:
  - Autosomal dominant with variable penetrance
  - Pedigree analysis suggests genetic heterogeneity
  - Multigenic mechanisms (demonstrated in mice, Amendola et al, Endocrinology 146:5038, 2005)
The non-Mendelian line of thought

• Germline mutations rare (*Abramowicz et al, Thyroid 7:325, 1997*)
• Girls affected more often (*Devos et al, JCEM 84: 2502, 1999*)
• 92 % of MZ twins discordant (*Perry et al, JCEM 87: 4072, 2002*):
  - Excludes Mendelian transmission (mono- or multigenic)
  - Makes environmental causes unlikely
• Twins: ↑ RR of CH 12-fold (*Medda et al, EJE 153: 765-73, 2005*)
• Proposed mechanisms:
  - Early somatic (i.e., post-zygotic) loss-of function mutation
  - Epigenesis: e.g., promoter methylation of the gene involved differs between twins
"Thyroid-specific" transcription factors

<table>
<thead>
<tr>
<th>Names</th>
<th>Family</th>
<th>Extrathyroid expression</th>
<th>Human Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTF1 T/ebp NKX2.1</td>
<td>Homeo-domain</td>
<td>•Lung</td>
<td>14q13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>•Forebrain</td>
<td></td>
</tr>
<tr>
<td>TTF2 FKHL15 FOXE1</td>
<td>Forkhead/Winged helix</td>
<td>•Palate</td>
<td>9q22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>•Rathke’s pouch</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>•Hair</td>
<td></td>
</tr>
<tr>
<td>PAX8</td>
<td>Paired domain box</td>
<td>•Kidney</td>
<td>2q12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>•Mid-hindbrain</td>
<td></td>
</tr>
</tbody>
</table>
TSHR appears too late to play a role in migration.

Thyroid migration and terminal differentiation

• During normal development, migration and terminal differentiation are mutually exclusive (migration has to be completed before terminal differentiation starts).

• However, when migration stops prematurely, terminal differentiation occurs, as shown by:
  - Ttf 2 -/- mice
  - Humans with ectopic thyroid
# Thyroid dysgenesis: K/O & mutations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mice (−/−)</th>
<th>Humans (+/− or −/−)</th>
</tr>
</thead>
</table>
| **TTF1** | • Athyreosis *(and no C-cells)*  
• Abnormal forebrain  
• Lung agenesis | • Mild ↑ TSH → ‘athyreosis’  
• ↓ tone → choreoathetosis  
• RDS, lung infections |
| **TTF2** | • Embryo: Ectopy in 1/2  
• Newborn: Athyreosis  
• Cleft lip and palate | • Athyreosis  
• Cleft palate  
• Kinky hair, bifid epiglottis |
| **PAX8** | • Athyreosis | • Orthotopic hypoplasia  
• ‘Athyreosis’ |

**Mice:** initial thyroid bud always forms, then disappears  
**Humans:** - ~ 20 with germline mutations among ~ 500 tested  
- no case with ectopy documented by scintigraphy
Thyroid dysgenesis: Why are mutations so rarely found?

• The disease is not Mendelian, so alternative mechanisms need to be considered
• The disease is primarily a defect in migration, so genes involved in cell migration may need to be considered
Migration of the thyroid

- The mechanisms regulating the dissociation of the median thyroid anlage from the pharyngeal endoderm and its further migration remain largely unknown.
- Is migration of the median thyroid bud:
  - Passive? (Fagman et al, Endocrinology 144: 3618, 2003)
- Thyroid ectopy = “Kallmann syndrome of the thyroid”? (but: Kallmann is Mendelian, thyroid dysgenesis generally is not)
Thyroid dysgenesis: The somatic mutation hypothesis

Somatic mutations in the transcription factors that are relatively specific for the thyroid, occurring early in embryogenesis, would be a plausible explanation for defects in thyroid differentiation and migration.
Critique of the hypothesis: conceptual

• All somatic mutations described so far are gain-of-function mutations and give the mutated cell a competitive advantage (proliferation, hyperfunction) over its neighbours.

• If a loss-of-function mutation occurs in one of the many (~100?) cells of the lingual thyroid bud, that cell may fail to migrate but all the others will → plausible only if it occurs early in embryogenesis (i.e., in the common ancestor of these ~100 cells).
Post-zygotic loss-of-function events can give a phenotype

- Monozygotic twins discordant for Turner’s syndrome (Reiss et al, Ann Neurol 34: 95, 1993)
- More generally, 45,X/46XX or 45,X/46,XY mosaicism
- Somatic mosaicism for androgen receptor gene mutations, giving a phenotype of partial androgen insensitivity syndrome (Köhler, Lumbroso et al, JCEM 90:106, 2005)
Critique of the hypothesis: technical

DNA fragmentation in paraffin-embedded thyroid (Ando et al, JCEM 87:3315, 2002)

B: Fresh leukocytes
F: Frozen thyroid
P: Paraffin-embedded thyroid

1kb
0.5kb
0.1kb
Critique of the hypothesis: practical - is it testable?

- One needs to compare the sequence of candidate genes in ectopic thyroid tissue and in leukocyte DNA from the same individual.
- Ectopic thyroid is no longer considered an indication for surgery.
  → how can fresh ectopic thyroid tissue be obtained?
TSH-dependent growth of ectopic thyroid cells

Before thyroxine treatment

After thyroxine treatment

(pictures courtesy of Drs Daniel Gunther and Catherine Pihoker, Seattle)
• Day 3: TSH 37 mU/L, T₄ 112 nM/L; Day 18: TSH 12 mU/L, T₄ 99 nM/L
• Lingual mass noted at age 5 years, voice changes at 8 years
• Scintigraphy: only thyroid present, TSH 6.61 mU/L, fT₄ 8.47 pmol/L
• No change after 9 months of L-T₄, therefore operated
Magnification X25, Hematoxylin-Phloxine-Safran staining (courtesy of Dr Luc L. Oligny, Dpt of Pathology, Ste-Justine Hosp.)

- Normal lingual mucosa
- Normal thyroid follicles
Somatic mutation vs epigenesis?

The size of founder cell populations in the embryo:
- is too low for the frequency of spontaneous somatic mutations to be a major issue in the morphogenesis of individuals.
- is more consistent with the frequency of errors generated by epigenetic controls such as methylation of nucleotides.

(Mathis and Nicolas, Trends in Genetics 18:627, 2002)


**TTF2: a good candidate for epigenetic regulation of thyroid migration?**

If it is, one would expect:

1. A promoter with a high CpG content, since methyltransferases specifically target cytosines within CpG dinucleotides

2. A differential methylation pattern of the promoter between thyroidal (normal gland/adenoma) and non-thyroidal (leukocytes) tissue in the same individual
Preliminary results: *in silico research*

CpG content of the TTF2 promoter is high.

Transcription start = +1973  
ATG start site = +2661

CpG content of the TTF2 promoter region using the web site www.ucsf.edu/urogenec
Summary

• The phenotypes of ectopy and athyreosis may result from different mechanisms or from a common event modulated by sexually dimorphic factors
• The mechanisms underlying the vast majority of defects in thyroid gland migration in humans are non-Mendelian
• Early somatic mutations are conceivable
• TTF2 is a candidate for epigenetic control of thyroid migration:
  - It is the only factor clearly linked to thyroid migration in mice
  - Its promoter has a high CpG content
Thyroid dysgenesis: why bother?

- It represents one of the remaining enigmas in the pathophysiology of thyroid diseases
  (Vassart & Dumont, Endocrinology 146:5035, 2005)
- Demonstrating non-Mendelian mechanisms:
  • would be important for genetic counseling
  • may shed light on other more complex and less easily treatable congenital malformations
Congenital Hypothyroidism: Optimizing outcome
Intellectual outcome in CH: before neonatal screening

- The mean IQ of affected children was 76, and 40% required special education
- Prognostic value of:
  - Bone age at diagnosis
  - Chronological age at starting treatment
CH and IQ in the pre-screening era: prognostic value of bone age

<table>
<thead>
<tr>
<th>BONE AGE</th>
<th>PRENATAL</th>
<th>BIRTH</th>
<th>1-3 M</th>
<th>6 M</th>
<th>9-12 M</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONSET OF THERAPY</td>
<td>0 1 3 6 9 12 15 18</td>
<td>m 1 3 5 10 18</td>
<td>yr 1 2 3</td>
<td>yr 1 2 3</td>
<td>yr 1 3 5</td>
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<td>I.Q.</td>
<td>140</td>
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<td></td>
<td>120</td>
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<td>20</td>
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</table>
"Sporadic cretinism" at 4 months: Too late to salvage the brain
Twin brothers at 14 days:
One has severe hypothyroidism: which one?
Is complete salvage of brain development possible with early postnatal treatment even in severe CH?

• To a great extent, the fetal brain is protected from insufficient T₄ production by the fetal thyroid through:
  - Local upregulation of type 2 deiodinase
  - Supply of maternal T₄ (Vulsma et al, NEJM 1989):
    • cord blood T₄ in athyreosis ~ 25-50 % of normal
    • this maternal T₄ disappears by 8-19 days
• On the other hand, loss of IQ estimated to be 0.5 points/postnatal day - loss may not be linear
Clinical aspects of CH

- Diagnosis suspected clinically in:
  - 4 of 81 cases in New England in 1976-1978*
  - 2 of 200 cases at Sainte-Justine in 1987-2003**

- Clinically diagnosed cases are:
  - particularly severe
  - at high risk for loss of IQ

- False negatives of biochemical screening may occur (e.g., fetal blood mixing between twins), so the diagnosis should be considered if the clinical presentation is suggestive

**Van Vliet and Czernichow, Semin Neonatol 9:75, 2004
CH is associated with high birth weight

<table>
<thead>
<tr>
<th>Centile</th>
<th>&lt; 5&lt;sup&gt;th&lt;/sup&gt;</th>
<th>&lt; 10&lt;sup&gt;th&lt;/sup&gt;</th>
<th>≥ 50&lt;sup&gt;th&lt;/sup&gt;</th>
<th>&gt; 90&lt;sup&gt;th&lt;/sup&gt;</th>
<th>&gt; 95&lt;sup&gt;th&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boys</strong></td>
<td>5%</td>
<td>11%</td>
<td>55%</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td>4%</td>
<td>9%</td>
<td>54%</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5%</td>
<td>10%</td>
<td>54%</td>
<td>14%*</td>
<td>9%*</td>
</tr>
</tbody>
</table>

*P<0.001 compared to national norms for sex and GA (Van Vliet et al, JCEM 88:2009, 2003)
% of CH newborns with absent knee epiphyses by sex and GA

- **Boys**
- **Girls**

Gestational age (weeks): 37, 38, 39, 40, 41, >=42

Normal newborns
Clinical message...

• In a newborn with unexplained postmaturity or macrosomia, it might be worth doing a knee X-ray and a plasma TSH if both knee epiphyses are absent.
• This may result in even earlier diagnosis than by biochemical screening.
• ...which may be important for developmental outcome in these severe cases.
Historical aspects of CH screening

• 1972: development of a radioimmunoassay for $T_4$ on eluates of filter paper bloodspots collected for PKU screening
  (J.H. Dussault, reviewed in JCEM 1999)

• 1977: serum thyrotrophin determination on day 5 of life as screening procedure for congenital hypothyroidism
  (Delange et al, Arch Dis Child 52: 89, 1977)
Blood collected by heel prick on filter paper on 2\textsuperscript{nd} or 3\textsuperscript{rd} day of life (earlier if: blood transfusion, death or transfer)

Samples sent to screening lab every weekday

Single measurement of TSH (results in mU/L of whole blood)

- **TSH <11**: N
- **TSH <15**: N
- **TSH 15-29**: measure T4 on initial spot
- **T4 N**

- **TSH ≥11**: repeat in duplicate on initial blood spot
  - **TSH ≥30**
  - **T4 low**
    - Call parents: Immediate referral

- Request 2\textsuperscript{nd} filter paper and refer if TSH ≥15 or T4 low
CH Evaluation - Québec, 2006

- History (family and personal), physical
- Plasma TSH, free T₄, total T₃ and anti-thyroperoxidase antibodies (mother+BB)
- ⁹⁹ᵐ Tc scan: head/neck/mediastinum (empty salivary glands by feeding)
- Plasma thyroglobulin level in baby
- X-ray of the left knee
Normal intellectual potential

Moderate CH

Risk of IQ loss

Severe CH
Intellectual outcome in CH

• CH is a heterogeneous condition: severity of disease influences outcome

• Severity of CH has been assessed by:
  - Bone age (knee and ankle): sexual dimorphism
  - Etiology (athyreosis > ectopy): scan-dependent
  - Plasma $T_4$ at diagnosis:
    • postnatal age-dependent
    • threshold effect
Tillotson et al, BMJ 309: 440, 1994

Graph showing the relationship between plasma thyroxine at diagnosis (nmol/l) and full scale IQ for non-manual and manual/unemployed groups. The graph includes data points and annotations A, B, and C.
Intellectual outcome in CH: after neonatal screening

• The early days:
  Patients with severe CH treated at 25-35 days with ~ 6 µg/kg.d. of levothyroxine still had clinically significant intellectual impairment (mean loss of 6-22 IQ points), while those with moderate CH were similar to (sibling) controls.

• The last 15 years:
  - Treatment started at a mean age of 9-14 days
  - Mean starting dose of 10-15 µg/kg.d at many centers
  - Is the gap between severe and moderate CH closed?
CH: Best starting dose of T4?

- 47 infants, birthweight 3 to 4 kg
- Born between 1995 and 2001, treated at 11 d (1-28)
- Randomized to:
  - 37.5 µg/day (N=15)
  - 62.5 µg/day for three days, then 37.5 µg/day (N=15)
  - 50 µg/day (corresponding to 14.5 µg/kg.day) (N=17)
- Endpoints: thyroid function at 3 days and at 1, 2, 4, 8, 12 weeks

(Selva et al, J Pediatr 141: 786, 2002)
**CH: Best starting dose of T₄?**

<table>
<thead>
<tr>
<th>Thyroxine dose (µg/day)</th>
<th>Mean TSH after 2 wks (mU/L)</th>
<th>Mean fT₄ after 2 wks (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37.5</td>
<td>38.9</td>
<td>35.6</td>
</tr>
<tr>
<td>62.5 X 3 days, then 37.5</td>
<td>29.4</td>
<td>39.1</td>
</tr>
<tr>
<td>50</td>
<td>4.8</td>
<td>56.3</td>
</tr>
</tbody>
</table>

Subjects who took longer than 2 weeks to normalize thyroid function had significantly lower cognitive, attention and achievement scores

*(Selva et al, J Pediatr 141:786, 2002 and 147:775, 2005)*
Intellectual development in CH: Ste-Justine cohort study, 1990-present

- Treatment started at a mean age of 14 days
- Initial dose 11.3±2.1 µg/kg.d. (mean ±SD)
- 9 patients with severe CH (Rx at 12-16 days)
- 9 with moderate CH (Rx at 10-26 d.) (controls)
- Groups matched for family education
- Exclusion: low APGAR, other problems
- Griffiths at 18 mos, Mc Carthy at 5 y 9/12
- Psychologist blinded to Dx subcategory
During treatment (severe, moderate), mean+SEM

**L-T₄ dose**

**TSH**

**fT₄**

**TotalT₃**
# IQ at school entry (mean±SD)

<table>
<thead>
<tr>
<th>CH subgroup</th>
<th>Previous cohort *</th>
<th>Present cohort **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe</strong></td>
<td>86±11 (n=12)</td>
<td>109±17 (n=9)</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>108±10 (n=15)</td>
<td>104±17 (n=9)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Glorieux et al, J Pediatr 121: 581, 1992
**Simoneau-Roy et al, J Pediatr 144: 748, 2004
**Development at 10-30 mo in CH:**
effect of early (<13 d) high-dose (>9.5 µg/kg.d)

<table>
<thead>
<tr>
<th></th>
<th>Sev. (n=27)</th>
<th>Mild (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early/High</td>
<td>123±9</td>
<td>120±13</td>
</tr>
<tr>
<td>Early/Low</td>
<td>109±8</td>
<td>123±12*</td>
</tr>
<tr>
<td>Late/High</td>
<td>101±10</td>
<td>117±7*</td>
</tr>
<tr>
<td>Late/Low</td>
<td>113±4</td>
<td>111±14</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

* P<0.005 for mild vs severe
Is transient "hyperT₄" harmful?

- No clinical signs and symptoms of hyperT₄ (normal T₃?)
- Rovet et al, J Peds 1989:
  - Greater temperamental difficulty between 6 and 24 months, related to higher plasma T₄ at 1 and 3 months *but*:
  - Higher plasma T₄ during infancy associated with better perceptual-motor skills at 3 years
- Not confirmed by Oerbeck et al, Arch Dis Child 2005
- Bongers-Schokking et al, J Peds 2005:
  - Overtreatment associated with supranormal IQ and verbal scores
  - Behavioral problems associated with:
    - Higher fT₄ at the time of testing
    - Later normalization of T₄ at start of therapy
Is transient "hyperT₄" harmful?

- No craniosynostosis
- Normal bone maturation at age 3 years
- Normal bone mineral density:
  - at age 8.5 years
  - at age 18 years
    Salerno M et al, Eur J Endocrinol 151:689, 2004
Complete salvage of the brain is possible even in severe CH

- Treat as early as possible (clinical sense!)
- The only randomized trial of $T_4$ dose supports the use of 50 µg/day as the initial dose in newborns weighing 3-4 kg
- Control TSH, $fT_4$, $T_3$ after ~ 3 weeks
- Guidelines for dose modifications?
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