Sessione Interattiva:
La Carenza Di Iodio In Eta’ Evolutiva

CLINICA E SVILUPPO PSICOMOTORIO

Roberto Gastaldi
IRCCS Giannina Gaslini, Genova
Embryology of Thyroid Gland

A. pharyngeal pouches
    - 1. 2. 3. 4.
    - laryngo-tracheal diverticulum
    - esophagus

B. oropharyngeal membrane
    - heart
    - branchial arches
    - foramen cecum
    - former site of oropharyngeal membrane

C. primitive pharynx
    - thyroid diverticulum
    - esophagus
    - foramen cecum
    - thyroglossal duct
    - site of atrophy
    - thyroid gland
    - hyoid bone

D. tongue
    - hyoid bone
    - palat
    - former tract of thyroglossal duct
    - larynx
    - pyramidal lobe
    - thyroid
Schematic view of thyroid morphogenesis

Fagman H, Nilsson M J Mol Endocrinol 2011
Changes in concentrations of maternal and fetal thyroid hormones in the fetal circulation during human gestation

Thyroid accumulates and binds iodide by the 11th-12th week

Chan SY, 2009 Nat Clin Pract Endocrinol Metab
T4 is transported to the brain thyroid hormone-binding proteins such as transthyretin (TTR), where T4 then passes out through endothelial cells lining the blood vessels.

T3 can reach the target neurons from the astrocytes, and directly from the extracellular matrix.

Indirect effects of thyroid hormone on neuronal differentiation through astrocytes
TR and T3 in the human fetal brain

weight (g)

TH-R concentration (fmol/mg DNA)

TH-R in brain T3 on TH-R (fmoles / brain)

weeks of gestation

r = 0.995

r = 0.989

50-fold

10^5

r = 0.990

500-fold

Postnatal morphological changes in the rodent cerebellum after neonatal hypothyroidism

Berbel P: Behav Brain Res. 1994.
Myelination in the anterior commissure of euthyroid and hypothyroid rats.

Berbel P: Behav Brain Res. 1994.
<table>
<thead>
<tr>
<th>Age</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Spontaneous abortions, Still births, Mal development of fetal brain, Birth of cretins</td>
</tr>
<tr>
<td>Childhood</td>
<td>Goiter, Low IQ, Impaired learning, Mental retardation, Delayed motor development, Stunted growth, Apathy, Muscular disorders, Paralysis, Speech &amp; hearing defects, High perinatal mortality, High infant mortality</td>
</tr>
<tr>
<td>Adolescent</td>
<td>Mental retardation, Growth retardation</td>
</tr>
<tr>
<td>Adult &amp; all ages</td>
<td>Goiter, Hypothyroidism, Apathy, Impaired mental function, Reduced work output</td>
</tr>
</tbody>
</table>
Neurological cretinism

- Associated with severe iodine deficiency and is more prevalent in countries with low iodine in the diet
- Most common type of cretinism world-wide
- Severe mental retardation
- Deafness and mutism
- Squinting
- Diplegia
- Goiters and thyroid gland dysfunction may be present in this type of cretinism, but they are not necessary for the identification.
Hypothyroid cretinism

- Severe hypothyroidism
- Mental retardation (which is less severe than in neurological cretinism)
- Dwarfism and retarded maturation
- Large Anterior Fontanelle and/or Posterior Fontanelle >0.5 cm
- Thick skin
- Delayed reflexes
- Hypotonia
- Lethargia
- Prolonged jaundice
- Large Tongues
- Hoarse cry
- Umbilical hernia
- Bradycardia and low voltage QRS complexes


**Effect of Age at The Beginning of Treatment on Mean IQ Scores**

<table>
<thead>
<tr>
<th>WPPSI-R</th>
<th>Age at the beginning of treatment</th>
<th>Group 2 (n = 11)</th>
<th>Group 3 (n = 10)</th>
<th>Group 2 (n = 10)</th>
<th>Group 3 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;21 days</td>
<td></td>
<td></td>
<td>&gt;21 days</td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>98 ± 10</td>
<td>98 ± 8</td>
<td>93 ± 9</td>
<td>98 ± 11</td>
<td></td>
</tr>
<tr>
<td>Performance IQ</td>
<td>95 ± 11</td>
<td>99 ± 7</td>
<td>90 ± 10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>98 ± 7</td>
<td></td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>96 ± 10</td>
<td>98 ± 7</td>
<td>91 ± 10</td>
<td>98 ± 9</td>
<td></td>
</tr>
<tr>
<td>Age at treatment (days)</td>
<td>17 ± 2</td>
<td>16 ± 3</td>
<td>28 ± 2</td>
<td>26 ± 3</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup><sup>p</sup> < 0.05 vs. group 3.

LT<sub>4</sub>, levothyroxine; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence-Revised.
<table>
<thead>
<tr>
<th></th>
<th>Total (n = 63)*</th>
<th>Athyrosis (n = 26)</th>
<th>Dysgenesis (n = 33)</th>
<th>Controls (n = 175)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td></td>
<td>mean (SD)</td>
<td>mean (SE)</td>
<td>mean (SD)</td>
<td>mean (SE)</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>99.4 (11.9)</td>
<td>101.7 (1.4)‡</td>
<td>95.8 (11.6)</td>
<td>98.7 (2.1)‡</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>98.8 (10.9)</td>
<td>102.2 (1.3)‡</td>
<td>96.9 (10.6)</td>
<td>100.9 (2.0)‡</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>100.2 (12.9)</td>
<td>100.8 (1.5)‡</td>
<td>95.6 (11.7)</td>
<td>96.5 (2.3)‡</td>
</tr>
</tbody>
</table>

* Because the number of children in the dysshromonogenesis group was small (n = 4), they were excluded from subgroup analysis.

Comparison for adjusted values:

‡ p ≤ 0.05 comparison between dysgenesis and athyrosis.

‡ p < 0.001, § p ≤ 0.01 comparison to controls (ANCOVA and multiple comparisons after Tukey, level of significance).

SE, standard error; WISC-R, Wechsler Intelligence Scale for Children, Revised version.
Final IQ outcome in children with congenital hypothyroidism treated with levothyroxine

<table>
<thead>
<tr>
<th>Study</th>
<th>n (patients/controls)</th>
<th>Duration (years)</th>
<th>Start of treatment (days of life)</th>
<th>Levothyroxine dose (µg/kg daily)</th>
<th>Full-scale IQ controls</th>
<th>Full-scale IQ CH patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oerbeck et al.⁷⁹</td>
<td>49/41 (siblings)</td>
<td>20</td>
<td>24.4</td>
<td>8.4</td>
<td>111.4</td>
<td>102.4</td>
</tr>
<tr>
<td>Rovet et al.⁷⁸</td>
<td>42/42 (siblings)</td>
<td>6-9</td>
<td>12.8 (7.6-18)</td>
<td>3.2-12.3</td>
<td>108.9</td>
<td>102.7</td>
</tr>
<tr>
<td>Dimitropoulos et al.⁸⁴</td>
<td>63/175 (normal control group)</td>
<td>14</td>
<td>9 (5-18)</td>
<td>14.7 (9.9-23.6)</td>
<td>111.4</td>
<td>101.7</td>
</tr>
</tbody>
</table>

L-Thyroxine treatment and QSPM score

- **QSPM**
  - 100.6 ± 10.7

- **L-Thyroxine 8-10 mcg/kg**
  - 19

- **L-Thyroxine 10-12 mcg/kg**
  - 31

- **QSPM**
  - 102.1 ± 10.4

Gastaldi R, 2009
Means for Child Cognitive Outcomes According to maternal Iodine Status in the First Trimester

- **Verbal IQ**
  - p=0.002

- **Total IQ**
  - p=0.04

- **Reading accuracy**
  - p=0.06

- **Reading comprehension**
  - p=0.04

**Maternal iodine-to-creatinine ratio (µg/g) in the first trimester**

Bath SC, The Lancet 2013
Effect of Maternal Iodine Supplementation on neurodevelopmental Indices in the Child

<table>
<thead>
<tr>
<th>Maternal iodine intake/day</th>
<th>No</th>
<th>Infant score</th>
<th>P value</th>
<th>Country; reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>KI 200 µg from 4 to 6 weeks</td>
<td>n=13</td>
<td>101.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT₄ &gt; 20th percentile</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Group 2:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KI 200 µg from 12 to 14 weeks</td>
<td>n=12</td>
<td>92.2</td>
<td>P&lt;0.05ᵃ</td>
<td>Alicante, Spain (36)</td>
</tr>
<tr>
<td>FT₄ 0–10th percentile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group 3:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KI 200 µg from 37 to 40 weeks</td>
<td>n=19</td>
<td>87.5</td>
<td>P&lt;0.001ᵇ</td>
<td></td>
</tr>
<tr>
<td>FT₄ 0–10th percentile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Developmental quotient

Taylor P N Eur J Endocrinol 2014
Inadequate iodine status during early pregnancy is adversely associated with child cognitive development.

Maternal hypothyroxinemia in the first half of pregnancy is a risk factor for poor cognitive functioning in infancy and childhood.

Iodine supplementation improves some maternal thyroid indices and may benefit aspects of cognitive function in school-aged children even in marginally iodine-deficient areas.
Ministero della Salute

L’uso in cucina e a tavola di sale arricchito di **iodio** assicura a tutti la giusta quantità di **iodio**, fondamentale per la crescita del bambino e la prevenzione di molti disturbi della tiroide.

**Un pizzico di SALUTE per TUTTI? SALE ARRICCHITO DI IODIO!**

**RICORDA CHE IL SALE VA AGGIUNTO CON MODERAZIONE**
molti prodotti alimentari lo contengono già.
Società Italiana di Endocrinologia E Diabetologia Pediatrica (SIEDP)

PROGETTO ITALIANO CONTRO LA CARENZA IODICA IN PEDIATRIA (PICCIP)

............Coming soon
Grazie per l’attenzione