Effects of IUGR on fetal brain development

Challenges and Opportunities

Eduard Gratacos
Maternal-Fetal Medicine Department and Research Center
Hospital Clinic - University of Barcelona

www.medicinafetalbarcelona.org
1. Brain and fetal life
2. Specific effects of IUGR on neurodevelopment
3. Brain effects of IUGR
4. Clinical implications
1. Brain and fetal life

2. Specific effects of IUGR on neurodevelopment

3. Brain effects of IUGR

4. Clinical implications
Fetal programming
Brain reorganization
(+/- injury)
Neurocognitive disorders/Learning disabilities
Overall ≥10%
Estimated 2/3 of prenatal origin

Non-specific disorders
5-8%

Attention Deficit Hyperactivity Disorder
2-5%

Autism Spectrum Disorder
0.5-1%
1. Brain and fetal life

2. Specific effects of IUGR on neurodevelopment

3. Brain effects of IUGR

4. Clinical implications
IUGR is associated with a higher frequency of ultrasound brain lesions and abnormal neonatal neurobehaviour.

<table>
<thead>
<tr>
<th></th>
<th>IUGR</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (fetuses)</td>
<td>90</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>GA at birth (wks)</td>
<td>31.2 (2.4)</td>
<td>31.1 (2.4)</td>
<td>0.73</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>1078</td>
<td>1616</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* p<0.05

Cruz et al. 2010

www.fetalmedicinebarcelona.org/
Early-onset IUGR

PROBLEM #2: (NEUROLOGICAL) MORBIDITY

Brain US anomalies in 30w IUGR

Perinatal Mortality

>90%  30-40%  <10%

Fouron 2004
Del Rio 2008
Cruz-Martinez 2012

www.fetalmedicinebarcelona.org/
Dichorionic Twins. Born 34 weeks
Twin 1: 1950 g (p45)
Twin 2: 1200 g (p1). Normal Doppler

Lagercrantz H. Better born too soon than too small.
Lancet 1997

Satchev, 2012
Figueras 2006-2011
Baschat 2009, 2011
Vohr 2004
Geva 2002-2011
Marsal 00-06
Visser 01-11
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EFFECTS OF IUGR ON THE FETAL BRAIN

MICROSTRUCTURE METABOLISM

CORTICAL DEVELOPMENT

CONNECTIVITY
MODEL: White Matter Damage

Normal acoustic signature

WMD acoustic signature

Correlation Between a Semiautomated Method Based on Ultrasound Texture Analysis and Standard Ultrasound Diagnosis Using White Matter Damage in Preterm Neonates as a Model

J Ultrasound Med 2011
Fetal Diagn Ther 2012
Am J Obstet Gynecol 2012
NEURO-METABOLOME PROJECT
Metabolites and neural function-maturation:
- **N-acetyl-aspartate (NAA):** Neuronal marker.
- **Choline (Cho):** Myelination and cell membrane turnover
- **Creatine (Cre):** Cellular energy
- **Myo-Inositol (Myo-Ino):** Glial marker. Osmoregulation
<table>
<thead>
<tr>
<th>Compound</th>
<th>p (Corr)</th>
<th>Mass</th>
<th>Description / biological function</th>
<th>Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparagine</td>
<td>0.0000242</td>
<td>132,0534</td>
<td>Amino acid required for the production of proteins concerned with development of nerves, and the transmission of impulses across nerve endings. Involved in the metabolic control of cell functions in nerve and brain tissue.</td>
<td>Down</td>
</tr>
<tr>
<td>Ornithine</td>
<td>0.0000275</td>
<td>132,0894</td>
<td>Amino acid that plays a role in the urea cycle.</td>
<td>Down</td>
</tr>
<tr>
<td>Palmitoleic acid</td>
<td>0.0000072</td>
<td>254,2249</td>
<td>Fatty acid, found in the brain.</td>
<td>Up</td>
</tr>
<tr>
<td>3-Nitrotyrosine</td>
<td>0.0000514</td>
<td>226,0599</td>
<td>Marker of oxidative stress specifically for protein nitration.</td>
<td>Down</td>
</tr>
<tr>
<td>N-Acetylaspartylglutamic acid</td>
<td>0.0006322</td>
<td>304,0914</td>
<td>Neuropeptide consisting of N-acetylaspartic acid (NAA) and glutamic acid coupled via a peptide bond. The third-most-prevalent neurotransmitter in the mammalian nervous system.</td>
<td>Down</td>
</tr>
<tr>
<td>GMP</td>
<td>0.0015353</td>
<td>363,0578</td>
<td>Regulator of ion channel conductance, glycogenolysis, and cellular apoptosis. It also relaxes smooth muscle tissues in blood vessels, leading to vasodilation.</td>
<td>Up</td>
</tr>
<tr>
<td>Histidine</td>
<td>0.0020271</td>
<td>155,0695</td>
<td>Amino acid.</td>
<td>Down</td>
</tr>
<tr>
<td>Docosahexaenoic acid</td>
<td>0.0022431</td>
<td>328,2408</td>
<td>A fatty acid of the human brain (cerebral cortex), essential for the growth and functional development of the brain.</td>
<td>Up</td>
</tr>
<tr>
<td>N-acetylaspartate</td>
<td>0.0022431</td>
<td>175,0482</td>
<td>NAA is the second-most-concentrated molecule in the brain after the amino acid glutamate. It is detected in the adult brains only in neurons synthesized in the mitochondria of neurons from the amino acid aspartic acid and acetyl-coenzyme A.</td>
<td>Down</td>
</tr>
<tr>
<td>Purine</td>
<td>0.0023747</td>
<td>120,0426</td>
<td>Component of biomolecules (ATP, GTP, cyclic AMP, NADH, coenzyme A). Purine may function directly as neurotransmitters, acting upon purinergic receptors. (Found to be an endogenous neuroprotectant in hypoxic brain)</td>
<td>Down</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>0.0031716</td>
<td>282,2564</td>
<td>Fatty acid, the most common fatty acid of myelin.</td>
<td>Up</td>
</tr>
<tr>
<td>L- Lysine</td>
<td>0.0038920</td>
<td>146,1056</td>
<td>Essential amino acid.</td>
<td>Down</td>
</tr>
<tr>
<td>Pantothenate</td>
<td>0.0038920</td>
<td>219,1108</td>
<td>Used in the synthesis of coenzyme A (CoA). CoA is important in energy metabolism.</td>
<td>Down</td>
</tr>
<tr>
<td>Malondialdehyde</td>
<td>0.0046385</td>
<td>72,02118</td>
<td>Marker for oxidative stress (ROS), results of lipid peroxidation.</td>
<td>Down</td>
</tr>
<tr>
<td>Succinate</td>
<td>0.0051832</td>
<td>118,0267</td>
<td>Succinate plays a biochemical role in the citric acid cycle.</td>
<td>Down</td>
</tr>
</tbody>
</table>
EFFECTS OF IUGR ON THE FETAL BRAIN

MICROSTRUCTURE
METABOLISM

CORTICAL DEVELOPMENT

CONNECTIVITY
Altered small-world topology of structural brain networks in infants with intrauterine growth restriction and its association with later neurodevelopmental outcome


Bataille 2012
Eixarch 2012
EFFECTS OF IUGR ON THE FETAL BRAIN

MICROSTRUCTURE
METABOLISM

CONNECTIVITY

CORTICAL DEVELOPMENT
IUGR IS ASSOCIATED WITH REDUCED DEEPER FISSURES

<table>
<thead>
<tr>
<th></th>
<th>Case (N=31)</th>
<th>Control (N=19)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD</td>
<td>95.33±2.95</td>
<td>100.64±3.23</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left_Insular_Depth</td>
<td>0.30±0.06</td>
<td>0.27±0.02</td>
<td>0.021</td>
</tr>
<tr>
<td>Right_Insular_Depth</td>
<td>0.3±0.07</td>
<td>0.27±0.03</td>
<td>0.16</td>
</tr>
<tr>
<td>Left_Sylvian_Fiss</td>
<td>0.16±0.05</td>
<td>0.14±0.03</td>
<td>0.37</td>
</tr>
<tr>
<td>Right_Sylvian_Fiss</td>
<td>0.15±0.04</td>
<td>0.15±0.03</td>
<td>0.57</td>
</tr>
<tr>
<td>Left_PO_Fiss</td>
<td>0.13±0.03</td>
<td>0.11±0.04</td>
<td>0.09</td>
</tr>
<tr>
<td>Right_PO_Fiss</td>
<td>0.14±0.04</td>
<td>0.11±0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Left_Cing_Fiss</td>
<td>0.09±0.02</td>
<td>0.09±0.02</td>
<td>0.79</td>
</tr>
<tr>
<td>Right_Cing_Fiss</td>
<td>0.09±0.02</td>
<td>0.09±0.02</td>
<td>0.98</td>
</tr>
<tr>
<td>Left_Calc_Fiss</td>
<td>0.18±0.03</td>
<td>0.16±0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>Right_Calc_Fiss</td>
<td>0.18±0.04</td>
<td>0.16±0.05</td>
<td>0.11</td>
</tr>
<tr>
<td>L/R Insular ratio</td>
<td>1.03±0.29</td>
<td>0.95±0.1</td>
<td>0.05</td>
</tr>
</tbody>
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SEVERE IUGR: TARGETED NEUROSONOGRAPHY
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BIOLOGIC PROGRAMMING AND AGE

Early and Late-Onset IUGR

IMPACT OF ENVIRONMENT

OPPORTUNITY FOR CORRECTION

Fetus  Child  Young  Mature  Old
4P medicine
- Predictive
- Preventive
- Personalized
- Participatory

Problem evident
4P medicine
- Predictive
- Preventive
- Personalized
- Participatory
1. Fetal life is a critical moment for brain reorganization.

2. IUGR induces specific effects and is possibly the most prevalent cause

3. IUGR changes affect all levels (macro-microstructure, metabolism, connectivity)

4. Brain biomarkers for ND will be used in future fetal medicine-neonatology