Fetal Programming

Impact of prenatal events on the brain and the heart

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Guillem was born at Maternitat (Hospital Clínic) with a diagnosis of mild fetal growth restriction. You even offered us to participate in a study of brain MRI.

Now he is almost 4 and he is suffering:
- Language disorders
- Motor delay
- Maturational delay
- Irritable mood with intolerance to frustration

Do you think these problems were caused by the problem of fetal growth restriction? Do you think this might cause further problems?

We remain awaiting your news,
Neonatal and Fetal GA-adjusted “normal” weight in the same population
Fetal growth restriction (and other disorders associated with disease or abnormal environment)

Adaptation = Epigenetics = Permanent “programming”
Dichorionic Twins. Born 34 weeks
Twin 1: 1950 g (p45)
Twin 2: 1200 g (p1). Normal Doppler

Bayley Score

- cognitive
- language
- motor
- socio-emot
- adaptive behavior

Satchev, 2012
Figuera 2006-2011
Baschat 2009, 2011
Vohr 2004
Geva 2002-2011
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%
IMPROVING NEURODEVELOPMENTAL DISORDERS OF FETAL ORIGIN
NOVEL RESEARCH LINES

IMPROVING DETECTION

NEW IMAGING BIOMARKERS

NEW THERAPIES
VIRTUAL MULTI-SCALE DISEASE MODELLING
INTEGRATED SYSTEMS-MEDICINE/BIOLOGY APPROACH TO BRAIN REMODELLING

IMAGING BIOMARKERS FOR CLINICAL PRACTICE
Multidisciplinary approach

Supradisciplinary approach: combined expertise for a single objective
EFFECTS OF IUGR ON THE FETAL BRAIN

MICROSTRUCTURE
METABOLISM

CONNECTIVITY

CORTICAL DEVELOPMENT
Ultrasound texture analysis (feature extraction + machine learning)

J Ultrasound Med 2011
Fetal Diagn Ther 2012
Am J Obstet Gynecol 2012
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

MRS validation of best candidates

Cell culture and experimental tissue markers

Experimental and Clinical MR-Spectroscopy

MRS: MAGNETIC RESONANCE SPECTROSCOPY

Sanz 2010

Van Vliet, PLoS 2012
Infants with IUGR show reduced connectivity.

**Background:** Children with attention-deficit disorders have impaired cortico-striato-thalamic connectivity.

Cortico-striato-thalamic right ipsilateral connectivity in infants with fetal growth restriction.
Fetal growth restriction
(and other disorders associated with disease or abnormal environment)
Adaptation = Epigenetics = Permanent “programming”
1986 Barker (MRC Unit, Southampton, UK):
Coronary heart disease mortality rates
FETAL CARDIOVASCULAR PROGRAMMING

INTRAUTERINE GROWTH RESTRICTION

fetal cardiac dysfunction

postnatal persistence of cardiovascular remodeling

hypertension, coronary disease, stroke, obesity, diabetes

cardiovascular disease in adulthood
IMPACT OF FETAL GROWTH ON CARDIOVASCULAR REMODELLING

Normal growth

IUGR

BP 90/65

cIMT = 0.386 mm

BP 115/80

cIMT = 0.434 mm
Fetal growth and molecular/ultrastructural remodelling

Shorter sarcomere length
Torre 2011, Iruretagoyena 2013

Protein expression and isoforms
Torre 2011, Tintu 2010

Titin isoforms:
• N2BA compliant
• N2B stiffer

Gene set analysis (FatiScan)
Data are median±SEM. *P<0.05 adjusted by GA, birthweight centile and preeclampsia
REVERTING CARDIOVASCULAR REMODELING

Experimental models

Molecular, gene and computer modeling

Epidemiology + Clin/Gene Prediction Kits + Intervention

CLÍNIC
Hospital Universitari

Sant Joan de Déu
Fetal growth restriction
(and other disorders associated with disease or abnormal environment)
Adaptation = Epigenetics = Permanent “programming”
BIOLOGIC PROGRAMMING AND AGE

IMPACT OF ENVIRONMENT

OPPORTUNITY FOR CORRECTION

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

- Identification of Risk
- Individual Biomarkers
- Intervention
- Window of Opportunity

Fetus to Child

Brain organization

Problem evident
fetal composite CV score for the prediction of postnatal hypertension
sensitivity 90%, specificity 77%

IDENTIFICATION OF RISK

INDIVIDUAL BIOMARKERS

INTERVENTION

WINDOW OF OPPORTUNITY

Fetus

Functional / structural organ remodeling

Problem evident

Cruz-Lemini FMF 2013, Skilton Pediatric 2012, Rodriguez 2013
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