Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

Differential vulnerability of gray matter and white matter to intrauterine growth restriction in preterm infants at 12 months corrected age

Nelly Padilla[a,f,g,*], Carme Junqué[e,f], Francesc Figueras[a,f,g], Magdalena Sanz-Cortes[a,f,g], Núria Bargalló[c,f], Angela Arranz[a,f,g], Antonio Donaire[d], Josep Figueras[b], Eduard Gratacos[a,f,g]

[a]Department of Maternal–Fetal Medicine, ICGON, Hospital Clínic, Universidad de Barcelona, C/Sabino de Arana 1, Helios III, 08028 Barcelona, Spain
[b]Department of Neonatology, ICGON, Hospital Clínic, Universidad de Barcelona, C/Sabino de Arana 1, 08028, Barcelona, Spain
[c]Department of Radiology, Centre de Diagnòstic per la Imatge (CDIC), Hospital Clínic, Universidad de Barcelona, C/Villarroel 170, 08036 Barcelona, Spain
[d]Department of Neurology, Institute of Neuroscience, Hospital Clínic, Universidad de Barcelona, C/ Villarroel 170, 08036 Barcelona, Spain
[e]Department of Psychiatry and Clinical Psychobiology, Faculty of Medicine, Universidad de Barcelona, C/ Casanova 143, 08036 Barcelona, Spain
[f]Institut D'investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), C/ Villarroel 170, 08036 Barcelona, Spain
[g]Centro de Investigación Biomédica en Enfermedades Raras (CIBERER), Corporació Sanitària Clínic, C/ Villarroel 170, 08036 Barcelona, Spain

ARTICLE INFO

Article history:
Accepted 6 December 2013
Available online 17 December 2013

Keywords:
Prematurity
Brain development
Gray matter development
White matter development
Voxel-based morphometry
Diffusion tensor imaging

ABSTRACT

Intrauterine growth restriction (IUGR) is associated with a high risk of abnormal neurodevelopment. Underlying neuroanatomical substrates are partially documented. We hypothesized that at 12 months preterm infants would evidence specific white-matter microstructure alterations and gray-matter differences induced by severe IUGR. Twenty preterm infants with IUGR (26–34 weeks of gestation) were compared with 20 term-born infants and 20 appropriate for gestational age preterm infants of similar gestational age. Preterm groups showed no evidence of brain abnormalities. At 12 months, infants were scanned sleeping naturally. Gray-matter volumes were studied with voxel-based morphometry. White-matter microstructure was examined using tract-based spatial statistics. The relationship between diffusivity indices in white matter, gray matter volumes, and

Abbreviations: AGA, Appropriate for gestational age; AD, Axial diffusivity; CA, Corrected age; DARTEL, Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra; DTI, diffusion tensor imaging; FA, fractional anisotropy; FWE, family-wise error; GM, gray matter; IUGR, intrauterine growth restriction; MD, mean diffusivity; MRI, magnetic resonance imaging; RD, radial diffusivity; SGA, small for gestational age; TBSS, tract-based spatial statistics; VBM, voxel-based morphometry; WM, white matter

*Corresponding author at: Universidad de Barcelona, Department of Maternal–Fetal Medicine, ICGON, Hospital Clínic, Sabino de Arana 1 – Helios III, 08028 Barcelona, Spain.
E-mail addresses: fpadilla@clinic.ub.es, nelly.padilla@ki.se (N. Padilla).

0006-8993/$ - see front matter
http://dx.doi.org/10.1016/j.brainres.2013.12.007

perinatal data was also investigated. Gray-matter decrements attributable to IUGR comprised amygdala, basal ganglia, thalamus and insula bilaterally, left occipital and parietal lobes, and right perirolandic area. Gray-matter volumes positively correlated with birth weight exclusively. Preterm infants had reduced FA in the corpus callosum, and increased FA in the anterior corona radiata. Additionally, IUGR infants had increased FA in the forceps minor, internal and external capsules, uncinate and fronto-occipital white matter tracts. Increased axial diffusivity was observed in several white matter tracts. Fractional anisotropy positively correlated with birth weight and gestational age at birth. These data suggest that IUGR differentially affects gray and white matter development preferentially affecting gray matter. At 12 months IUGR is associated with a specific set of structural gray-matter decrements. White matter follows an unusual developmental pattern, and is apparently affected by IUGR and prematurity combined.

1. Introduction

Intrauterine growth restriction (IUGR) is one of the common reasons indicated for preterm delivery. This condition, due to placental insufficiency, affects 5–10% of all pregnancies and is associated with chronic hypoxia and under-nutrition during fetal life. The combination of preterm birth and IUGR results in a higher rate of perinatal complications and consequently worse long-term outcomes (Geva et al., 2006; Guellec et al., 2011; Leitner et al., 2007).

The structural alterations underlying the effects of IUGR on the preterm brain are only partially documented. In this respect, studies have been hampered by the widespread practice of using the terms small for gestational age (SGA) and IUGR synonymously. Defining SGA as a birth weight (BW) below a given threshold compared to appropriate for gestational age (AGA) groups, SGA children had smaller brain volumes (De Bie et al., 2011; Martinussen et al., 2009; Xydis et al., 2013) and altered white matter (WM) microstructure (Eikenes et al., 2012; Lepomaki et al., 2013). In contrast, comparisons between preterm neonates with and without intrauterine growth restriction, defined as BW below the 10th percentile and abnormal Doppler values within the umbilical artery, showed that IUGR is associated with reduced volumes of the cortical gray matter (GM; Tolsa et al., 2004), decreased volumes of the hippocampus (Lodygensky et al., 2008) and a discordant pattern of gyrification (Dubois et al., 2008) related to behavioral alterations. At 12 months, comparisons between preterm infants with and without growth restriction and term-born controls suggested that the most pronounced differences in the IUGR preterm group were related to a different distribution of the GM and WM (Padilla et al., 2011) as well as a different cortical brain complexity (Esteban et al., 2010), both associated to neurodevelopmental difficulties. However, the GM alterations induced by IUGR, and the existence of microstructural WM differences, in preterm infants at 12 months, excluding the influence of prematurity itself, have not been investigated.

The aims of this study were (1) to detect specific regional GM volume changes as a consequence of IUGR in preterm infants at 12 months corrected age (CA); (2) to explore whether IUGR induces specific WM microstructure alterations

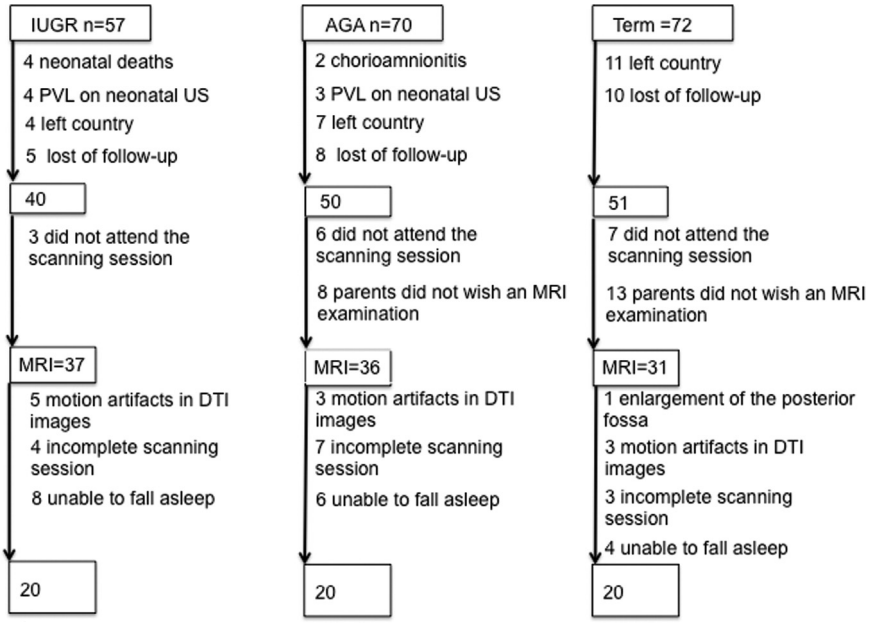

Fig. 1 – Study population. IUGR, intrauterine growth restriction; AGA, appropriate for gestational age; PVL, periventricular leukomalacia; US, ultrasound; DTI, diffusion tensor imaging; MRI, magnetic resonance imaging.