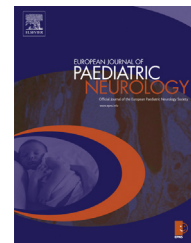




Official Journal of the European Paediatric Neurology Society



## Original article

# Region-specific reduction in brain volume in young adults with perinatal hypoxic-ischaemic encephalopathy



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## ARTICLE INFO

## Article history:

Received 3 January 2013

Received in revised form

29 April 2013

Accepted 9 May 2013

## Keywords:

Hypoxia-ischaemia

Perinatal brain injury

Very longterm follow-up

MRI-volumetry

Development

## ABSTRACT

**Background:** A severe form of perinatal hypoxic-ischaemic encephalopathy (HIE) carries a high risk of perinatal death and severe neurological sequelae while in mild HIE only discrete cognitive disorders may occur.

**Aim:** To compare total brain volumes and region-specific cortical measurements between young adults with mild-moderate perinatal HIE and a healthy control group of the same age.

**Methods:** MR imaging was performed in a cohort of 14 young adults (9 males, 5 females) with a history of mild or moderate perinatal HIE. The control group consisted of healthy participants, matched with HIE group by age and gender. Volumetric analysis was done after the processing of MR images using a fully automated CIVET pipeline. We measured gyrification indexes, total brain volume, volume of grey and white matter, and of cerebrospinal fluid. We also measured volume, thickness and area of the cerebral cortex in the parietal, occipital, frontal, and temporal lobe, and of the isthmus cinguli, parahippocampal and cingulate gyrus, and insula.

**Results:** The HIE patient group showed smaller absolute volumetric data. Statistically significant ( $p < 0.05$ ) reductions of gyrification index in the right hemisphere, of cortical areas in the right temporal lobe and parahippocampal gyrus, of cortical volumes in the right temporal lobe and of cortical thickness in the right isthmus of the cingulate gyrus were found. Comparison between the healthy group and the HIE group of the same gender showed statistically significant changes in the male HIE patients, where a significant reduction was found in whole brain volume; left parietal, bilateral temporal, and right parahippocampal gyrus cortical areas; and bilateral temporal lobe cortical volume.

**Conclusions:** Our analysis of total brain volumes and region-specific corticometric parameters suggests that mild-moderate forms of perinatal HIE lead to reductions in whole brain volumes. In the study reductions were most pronounced in temporal lobe and parahippocampal gyrus.

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<http://dx.doi.org/10.1016/j.ejpn.2013.05.005>

## 1. Introduction

The number of young adults growing up with chronic diseases of childhood or with consequences of acute disease is increasing due to improved treatment. Perinatal hypoxic brain injury and hypoxic-ischaemic encephalopathy (HIE) is a commonly recognized cause of severe, long-term neurological deficits in children.<sup>1</sup> Neonatal encephalopathy occurs with the incidence of 1–6/1000.<sup>2</sup> Among newborns affected by perinatal brain injury, 20–50% die during the newborn period, while 25–60% of the survivors suffer from permanent neurodevelopmental handicap, including cerebral palsy, seizures, feeding and communication impairment, mental retardation, and learning disabilities.<sup>2–5</sup>

Magnetic resonance imaging (MRI) serves as a useful tool for the measurement of potential biomarkers<sup>6</sup> of normal and altered brain development. MRI of neonates is required in order to obtain accurate information about the lesion, the timing of injury and to recognize the pattern of injury.<sup>7,8</sup> In addition, new tools for MRI analysis and magnetic resonance spectroscopy (MRS) can detect some biomarkers, predicting neurodevelopmental outcome.<sup>2,9–11</sup> Although there are numerous reports on HIE changes in newborns that were detected using MRI and studying their developmental outcomes and reports on individual brain structures,<sup>12</sup> our study is the first one to report the bioimaging markers of the whole brain of young adults who had perinatal HIE. Long term follow up of developmental trajectories in these children provides valuable information for the medical community.

Decades ago, MRI was not routinely available and distinguishing between children with different severity of brain injury was only possible through clinical evaluation. The grading system of Sarnat and Sarnat<sup>13</sup> still enables the classification of infants with HIE into three categories of severity: mild, moderate, and severe. Mild hypoxia-ischaemia can lead to minor disabilities, while moderate hypoxia-ischaemia can lead to motor impairment, and severe HIE to major handicap and death.<sup>14,15</sup>

To determine the long-term impact of mild to moderate HIE on brain development and structural organization, we compared volumetric MRI data of our young adult patients who had a history of perinatal HIE with healthy, by age and gender matched adults who were born at term and never hospitalized. Our hypothesis was that mild to moderate HIE, which is often associated with discrete learning and cognitive difficulties without severe motor or sensory impairment, is associated with the volume reduction in young adulthood, especially in the temporal and frontal lobes which are involved in cognition and memory.

## 2. Material and methods

### 2.1. Study locations

The study was performed at the University Children's Hospital, University Medical Centre Ljubljana, Slovenia, and at the Croatian Institute for Brain Research, School of Medicine, University of Zagreb, Croatia. The protocols were reviewed

and approved by the National Medical Ethical Committee of Slovenia. All scans were obtained and analysed at the Croatian Institute for Brain research, Zagreb, Croatia.

### 2.2. Conflict of interest statement

None of the authors had any financial interest in this manuscript.

### 2.3. Funding body agreements and policies

The study was funded by a grant from the Slovenian Research Agency ARRS 3311-03-831769 and ARRS-MS-HR-04-B/2008.

### 2.4. Ethics

The study was approved by the National Medical Ethical Committee of Slovenia. The participants were introduced to the study and provided informed consent. They were volunteers and did not receive any payment.

### 2.5. Subjects

Fourteen young adults, 9 male and 5 female, with a mean age of 22.1 years (standard deviation, SD = 0.70 years), who were born near term with a mean gestational age of 36.2 weeks (SD = 3.4 weeks) and a mean birth weight of 2719 g (SD = 746 g) were included in the study. They were born between 1988 and 1990, and admitted to the Neonatal Intensive Care Unit – NICU, University Medical Centre Ljubljana. Nine (64.3%) infants were admitted due to mild HIE, five (35.7%) infants due to moderate HIE. In females with HIE, three had a moderate and two had a mild form of HIE, while in males with HIE two had a moderate and seven had a mild form of HIE. The control group consisted of 14 healthy young adults, 9 male and 5 female, with a mean age of 22.8 years (SD = 0.71 years), who were born at term, healthy, without significant medical history. The groups were matched by age and gender. The healthy young adults were recruited from the local community.

Criteria for HIE included the following parameters: abnormal cardiocography, meconium, Apgar scores less than 7 at 5 min, need for resuscitation, cord pH less than 7.2 and base excess more than –15. The clinical assessment of HIE was done according to the Sarnat and Sarnat scoring<sup>13</sup>: mild, moderate, and severe HIE.

### 2.6. Imaging

Magnetic Resonance Imaging was done in the patient group at their age of 22.1 years (standard deviation, SD = 0.70 years), and in the healthy control group at 22.8 years (SD = 0.71), after clinical examination. We used a 3T Magnetom Trio Tim (Siemens), 12-channel head coil, standard clinical sequences that included sagittal 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with voxel size 1 mm × 1 mm × 1 mm and MPRAGE sequence parameters of: TR = 2300 ms; TE = 3 ms; flip angle 9°; matrix : 256 × 256.

Volumetric image processing was conducted by using the CIVET (version 1.1.11) pipeline developed at the ACE lab,

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