Official Journal of the European Paediatric Neurology Society

Original article

Quantification of ante-mortem hypoxic ischemic brain injury by post-mortem cerebral magnetic resonance imaging in neonatal encephalopathy

Paolo Montaldo [a,*], *Badr Chaban* [a], *Peter J. Lally* [a], *Neil J. Sebire* [b], *Andrew M. Taylor* [c], *Sudhin Thayyil* [a]

[a] *Centre for Perinatal Neuroscience, Imperial College London, Du Cane Road, London W12 0HS, United Kingdom*
[b] *Department of Histopathology, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London WC1 3JH, United Kingdom*
[c] *Centre for Cardiovascular Imaging, Institute of Cardiovascular Science, University College London, Gower Street, London WC1E 6BT, United Kingdom*

ARTICLE INFO

Article history:
Received 12 December 2014
Received in revised form
22 June 2015
Accepted 8 July 2015

Keywords:
Neonatal encephalopathy
Post-mortem
Magnetic resonance imaging

ABSTRACT

Post-mortem (PM) magnetic resonance imaging (MRI) is increasingly used as an alternative to conventional autopsy in babies dying from neonatal encephalopathy. However, the confounding effect of post-mortem changes on the detection of ante-mortem ischemic injury is unclear. We examined whether quantitative MR measurements can accurately distinguish ante-mortem ischemic brain injury from artifacts using post-mortem MRI.

Methods: We compared PM brain MRI (1.5 T Siemens, Avanto) in 7 infants who died with neonatal encephalopathy (NE) of presumed hypoxic-ischemic origin with 7 newborn infants who had sudden unexplained neonatal death (SUND controls) without evidence of hypoxic-ischemic brain injury at autopsy. We measured apparent diffusion coefficients (ADCs), T1-weighted signal intensity ratios (SIRs) compared to vitreous humor and T2 relaxation times from 19 predefined brain areas typically involved in neonatal encephalopathy.

Results: There were no differences in mean ADC values, SIRs on T1-weighted images or T2 relaxation times in any of the 19 predefined brain areas between NE and SUND infants. All MRI images showed loss of cortical gray/white matter differentiation, loss of the normal high signal intensity (SI) in the posterior limb of the internal capsule on T1-weighted images, and high white matter SI on T2-weighted images.

Conclusion: Normal post-mortem changes may be easily mistaken for ante-mortem ischemic injury, and current PM MRI quantitative assessment cannot reliably distinguish

Abbreviations: SUND, Sudden Unexplained Neonatal Death; NE, Neonatal Encephalopathy; PLIC, Posterior Limb of the Internal Capsule; DESTIR, Double-Echo Short Tau Inversion Recovery; FLASH, Fast Low Angle Shot; CISS, Constructive Interference in the Steady State; DWI, Diffusion-Weighted Imaging; ADC, Apparent Diffusion Coefficient; SIR, Signal Intensity Ratio; ROI, Region of Interest.

* *Corresponding author*. Centre for Perinatal Neuroscience, Level 5 Hammersmith House, Department of Paediatrics, Imperial College London, Du Cane Road, London W12 0HS, United Kingdom. Tel.: +44 203 313 8515.
E-mail address: p.montaldo@imperial.ac.uk (P. Montaldo).

http://dx.doi.org/10.1016/j.ejpn.2015.07.006

these. These findings may have important implications for appropriate interpretation of PM imaging findings, especially in medico-legal practice.

1. Introduction

Despite therapeutic hypothermia, a quarter of infants with neonatal encephalopathy still die in the UK and other high-income countries. Post-mortem (PM) examination in such cases is important to establish the etiology and timing of events, exclude underlying congenital defects that might recur, and to identify additional cerebral pathologies, for example intracranial bleeds.[1] Furthermore, birth asphyxia related brain injuries are of medico-legal significance and one of the most common reasons for obstetric litigation worldwide, and hence accurate identification of the cause of death and underlying pathology is important.[2] However, consented neonatal autopsy rates are currently less than 20% in the UK and other developed countries.[3] Therefore, there is increasing interest in using PM magnetic resonance imaging (MRI) for diagnosis of neuropathological lesions,[4–6] including hypoxic ischemic brain injury.[7,8] However, it remains uncertain whether ante-mortem ischemic changes can be reliably distinguished from changes occurring post-mortem.

The aim of this study was therefore to examine whether quantitative MR measurements can distinguish ante-mortem ischemic brain injury from post-mortem artifacts on post-mortem MRI.

2. Methods

This was a nested study as part of a large prospective study (MaRIAS – Magnetic Resonance Imaging Autopsy Study) comparing PM MRI with conventional autopsy in newborns.[9] The PM brain MRIs of seven infants who died following documented clinical neonatal encephalopathy (NE) of presumed hypoxic-ischemic origin were compared with those of seven infants who had sudden unexpected and unexplained death in the first seven days of life (SUND control)[10] without histological evidence of hypoxic-ischemic brain injury at autopsy. Infants with well-known risk factors, e.g., prematurity (<35 weeks gestation), perinatal asphyxia, or congenital malformations were classified as expected neonatal deaths and excluded.[10]

The NE cases and controls had matched gestation, post-mortem interval to MRI, and age at death. The MRI changes in the control group were therefore presumed to reflect post-mortem changes that have no clinical significance.

All scans were performed on a 1.5 Tesla MRI scanner (Siemens Avanto, Erlangen, Germany) using the same circularly polarized extremity coil. The following sequences were reported; 3D T1-weighted fast low angle shot (FLASH), 3D constructive interference in the steady state (CISS), 2D $T2^*$ weighted gradient echo, 2D diffusion-weighted imaging (DWI), and 2D T2-weighted double echo short tau inversion recovery (DESTIR). All 2D images were acquired in the axial plane [Table 1]. The bodies were kept in the mortuary at 4 °C and transported to the adjacent MR facility immediately prior to the MR scan.

A neonatologist with seven years of experience in post-mortem MRI and masked to the clinical history and autopsy findings reported the scans for evidence of hypoxic ischemic brain injury according to the scoring system described by Rutherford et al.[11,12] This included loss of normal high signal intensity in the posterior limb of the internal capsule (PLIC) (normal/loss/equivocal), abnormal signal intensity in the basal ganglia, loss of normal gray–white matter differentiation and focal cortical lesions, or diffuse or focal white matter injury [Fig. 1]. DWI was reported as normal, generalized abnormality or focal abnormality.

Regions of interest (ROI) (each measuring 48 to 50 mm^2) were delineated at 19 predefined brain locations to measure T1-weighted signal intensities, T2 relaxation times and apparent diffusion coefficients (ADCs). The brain regions assessed included: medulla oblongata, cerebellar peduncles, pons, mesencephalon, ventrolateral thalamus, rest of thalamus, globus pallidus, posterolateral putamen, rest of putamen, head of caudate nucleus, posterior limb of internal capsule, corona radiata, centrum semiovale, peri-Rolandic cortex, and visual cortex.[13–15] Regarding white matter structures, we examined: peripheral temporal white matter, peripheral occipital white matter, peripheral parietal white matter, and peripheral frontal white matter.[13]

T1-weighted intensity values were normalized to ocular vitreous signal intensity on the same image and analyzed as ratios (SIRs) to minimize differences in scaling, coil loading or other acquisition conditions, which affect signal intensity.[16] ADC values were obtained by tracing ROIs on the DESTIR images, on which the corresponding ADC maps were overlaid (Convert3D v1.0).

The following equation was used to calculate T2 relaxation times using the same ROI placed on both DESTIR images[17,18]:

$$T2 = (TE_2 - TE_1)/\ln(SI_1/SI_2)$$

where TE_1 and TE_2 are the echo times for the DESTIR images, and SI_1 and SI_2 represent the corresponding signal intensities in the region of interest.

Standard full autopsy was performed after MRI, including neuropathological examination by specialist pediatric pathologists masked to the MRI results with both macroscopic and microscopic examinations to include multiple regions of cortex, white matter, deep gray matter and posterior fossa structures. We did not co-register histological regions and MR ROI. Paraffin sections were stained by hematoxylin and eosin. Neuronal eosinophilia and karyorrhexis, astrocyte gliosis, activated microglia, accumulation of macrophages and hemorrhage were regarded as histopathological features of ischemic injury.[1,19] Edema was not included as a