Magnetic Resonance Imaging 62 (2019) 214–219

Contents lists available at ScienceDirect

Magnetic Resonance Imaging

journal homepage: www.elsevier.com/locate/mri

Original contribution

Neurite orientation dispersion and density imaging for evaluating the severity of neonatal hypoxic-ischemic encephalopathy in rats

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ARTICLE INFO

Keywords:
Diffusion tensor imaging
Hypoxic-ischemic encephalopathy
Magnetic resonance imaging
Neurite orientation dispersion and density imaging

ABSTRACT

Purpose: To evaluate the utility of neurite orientation dispersion and density imaging (NODDI) for longitudinally assessing neonatal hypoxic-ischemic (HI) encephalopathy severity with 7.0 T magnetic resonance imaging.
Methods: Thirteen 8-day-old Wistar rats underwent unilateral ligation of the left common carotid artery followed by mild (1 h; $n = 6$) or severe (2 h; $n = 7$) hypoxic exposure (8% O_2, 34 °C). Diffusion-weighted, T_2-weighted (T_2W), and flow-sensitive alternating inversion recovery images were obtained with a horizontal 7.0 T scanner at 1, 24, 72, and 168 h after HI insult. The fractional anisotropy (FA), apparent diffusion coefficient (ADC), intracellular volume fraction (ICVF), isotropic volume fraction (ISO), orientation dispersion index (ODI), and cerebral blood flow (CBF) values were calculated for each group (mild and severe) at each time point (1, 24, 72, and 168 h). ICVF, ISO, and ODI were the NODDI parameters.
Results: Left hemisphere brain damage was identified as slight hyperintensity on T_2W images after 1 h in both groups. In the severe group only, the signal hyperintensity increased time-dependently over 168 h. The ADC and CBF were not significantly different between the groups within any region. The ICVF and ODI were significantly higher in the severe vs. mild group at various points between 1 and 168 h (cortex, striatum, or white matter), whereas the FA was significantly higher in the mild vs. severe group at 168 h (cortex and white matter). The ISO was higher in the severe vs. mild group at 72 h (striatum) and 168 h (all regions), while the ISO was significantly higher in the mild vs. severe group at 24 h (all regions).
Conclusion: Here, ODI, a NODDI metric, identified early differences between mild and severe HI injuries. Our findings support the potential utility of NODDI for determining neonatal HI encephalopathy severity in rats.

1. Introduction

Hypoxic-ischemic encephalopathy (HIE), a major cause of neurologic disabilities [1], occurs in 1 to 3 per 1000 live full-term births and can result in long-term sequelae such as epilepsy and cerebral palsy [1,2]. Experimental rodent models of HIE are often used to study the pathology of this condition. Unilateral carotid artery ligation and exposure to hypoxia are commonly used to generate the HIE model [3–5]. In this model, prolonging the exposure time or increasing the temperature during hypoxia induces severe cerebral damage [6,7]. The severity of HIE is a key factor for determining the appropriate therapy. For instance, hypothermia, which is a standard treatment for HIE, is effective for mild, but not severe injuries [8,9]. Therefore, establishing a method that is capable of assessing the severity of HIE is necessary to ensure the appropriate treatment is provided.

Magnetic resonance imaging (MRI) is a sensitive imaging modality

Abbreviations: ADC, apparent diffusion coefficient; CBF, cerebral blood flow; DTI, diffusion tensor imaging; DW, diffusion - weighted; FA, fractional anisotropy; FAIR, flow sensitive alternating inversion recovery; HIE, hypoxic-ischemic encephalopathy; HI, hypoxic-ischemic; ICVF, intracellular volume fraction; ISO, isotropic volume fraction; MRI, magnetic resonance imaging; NODDI, neurite orientation dispersion and density imaging; ODI, orientation dispersion index; RARE, rapid acquisition with relaxation enhancement; SD, standard deviation; TE, echo time; TR, repetition time; T_2W, T_2-weighted

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https://doi.org/10.1016/j.mri.2019.07.013
Received 13 May 2019; Received in revised form 27 June 2019; Accepted 17 July 2019

that can noninvasively identify the brain damage generated by HI insult [10]. Diffusion tensor imaging (DTI) is an MRI technique that can measure the directional diffusivity of water. Quantitative DTI parameters, such as the fractional anisotropy (FA) and apparent diffusion coefficient (ADC), change depending on the stage of HIE severity [11]. However, the FA and ADC cannot be used to identify specific changes in water diffusion because such conventional DTI methods, which are based on a Gaussian distribution, use a single water compartment within each voxel [12]. This characteristic limits the absolute analysis of the water diffusion in cerebral tissues. Neurite orientation dispersion and density imaging (NODDI) is a new DTI approach introduced by Zhang et al. [13]. In the NODDI analysis, diffusing water in the brain is classified into the following three compartments: 1) intracellular compartment, 2) extracellular compartment, and 3) free diffusion in cerebrospinal fluid [12,13]. Using these classifications, quantitative maps for the intracellular volume fraction (ICVF), orientation dispersion index (ODI), and isotropic volume fraction (ISO) are generated. The ICVF, ODI, and ISO parameters denote diffusion restrictions within neurite membranes, diffusion disruptions owing to glial and neuronal cell bodies, and the isotropic Gaussian diffusion of cerebrospinal fluid, respectively [13]. Compared to using traditional DTI metrics, the use of these maps enables information that is more detailed to be obtained regarding the cerebral structure. Although it has been reported that NODDI demonstrated improved efficiency for evaluating microstructural alterations when applied in patients with human ischemic stroke [13], to the best of our knowledge, there are no reports on whether HI brain injury in neonatal rats can be quantitatively assessed using NODDI.

In this study, we used NODDI to longitudinally assess rats with mild or severe HIE and compared its efficacy with that of conventional DTI methods.

2. Materials and methods

2.1. Animal preparation

All animal experiments were approved by the Institutional Animal Care and Use Committee of our institution. The animals were permitted free access to food and water and were housed in a room maintained at a temperature of 23 °C and ~50% humidity. Thirteen 8-day-old Wistar rats (SLC, Shizuoka, Japan) underwent unilateral ligation and scission of the left common carotid artery under isoflurane inhalational anesthesia (3.0% for induction and 1.5–2.0% for maintenance) followed by 45 min of recovery. The rats were subsequently placed in a chamber that was set to reach an internal temperature of 34.0 °C and exposed to 8% oxygen for 1 or 2 h to generate the mild ($n = 6$) or severe ($n = 7$) injury group, respectively. The animals were euthanized by 5% isoflurane after the completion of all experiments.

2.2. MRI acquisition

The MRI was performed using a horizontal 7.0 T scanner (BioSpec 70/30 USR; Bruker Biospin, Ettlingen, Germany) with a 4-channel coil designed for the mouse brain at 1, 24, 72, and 168 h after HI insult. The rats were anesthetized by inhalational isoflurane (3.0% for induction and 1.5–2.0% for maintenance) and prostrated on a bed with mouth and ear bars to prevent any movements during the MR experiments [14] Body temperature was controlled with regulated water flow and continuously monitored using a physiological monitoring system (SA Instruments, Inc., Stony Brook, NY, USA). Diffusion-weighted (DW) and T_2-weighted (T_2W) images were obtained from the whole cerebrum.

Two-shell DW imaging was performed using multishot echo-planar imaging with the following parameters: repetition time (TR)/echo time (TE) = 3000/33 ms; number of slices = 10; slice thickness = 1 mm; field-of-view = 19.2 × 19.2 mm^2; matrix size = 128 × 128; number of shots = 4; fat suppression = on; slice orientation = transaxial; number of averages = 1; diffusion directions = 30; b-value shells = 0, 1000, and 2000 s/mm^2; partial Fourier transform acceleration = 1.5; zero filling factor = 1.3; and scan time = 13 min.

Anatomical T_2W images were acquired with a rapid acquisition with relaxation enhancement (RARE) sequence with the following parameters: TR/TE = 4000/33 ms; rare factor = 8; field-of-view = 19.2 × 19.2 mm^2; matrix size = 256 × 256; in-plane resolution = 75 × 75 μm^2; number of slices = 10; slice thickness = 500 μm; number of averages = 4; slice orientation = transaxial; and scan time = 6 min 20 s. These images were used to determine the accurate delineation of structures (same slice position as the DW images).

Flow-sensitive alternating inversion recovery (FAIR) images were acquired with a RARE sequence, as follows: TR/TE = 12,000/46 ms; rare factor = 72; field-of-view = 19.2 × 19.2 mm^2; number of slices = 1; matrix size = 128 × 128; in-plane resolution = 150 × 150 μm^2; slice orientation = transaxial; number of averages = 1; number of inversion times = 22 (30, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1950, 2100, and 2300 ms); and scan time = 7 min 40 s. A single transaxial slice was identified by referring to hyperintense regions on DW images.

2.3. Image analysis

The FA, ADC, and cerebral blood flow (CBF) were calculated by Paravision 5.1 (Bruker Biospin). The NODDI parameters, including the ICVF, ISO, and ODI, were calculated using MATLAB R2017b scripts (The MathWorks, Inc., Natick, MA, USA) and the NODDI toolbox (version 1.0.1; http://nitrc.org/projects/noddi_toolbox), as described previously [13]. The echo-planar images were corrected using the FSL eddy tool (ver. 5.0.11; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/eddy) for correcting eddy currents and movements in diffusion data [15]. All FA, ADC, ICVF, ISO, ODI, and CBF values were measured using Image J 1.51j (National Institutes of Health, Bethesda, MD, USA). Regions of interest were manually drawn on the cortex, white matter, and striatum of each hemisphere on DW images using the rat brain atlas by Paxinos and Watson [16] as a reference.

2.4. Statistical analysis

Data are presented as the mean ± the standard deviation. Differences were compared using analyses of variance followed by unpaired *t*-tests to compare the ipsilateral values between the two groups. All analyses were performed using Prism 5 (Version 5, GraphPad Software, CA, USA). Differences were considered statistically significant at $P < 0.05$.

3. Results

Representative FAIR images from the mild and severe groups at 1, 24, 72, and 168 h after HI injury are shown in Fig. 1. Compared to the contralateral CBF, the ipsilateral CBF in both groups appeared to reduce at 1 h after HI injury (Fig. 1A and E) and recover at 168 h after HI injury (Fig. 1D and H).

Representative T_2W images, DW images, FA maps, and ADC maps from the mild and severe groups at 1 and 168 h are shown in Fig. 2. At 1 h after HI insult, diminished ADC and hyperintensity on DW images were observed in the ischemic area compared to in the non-ischemic area in both groups (Fig. 2B, C, J, and K). Cerebral damage, as identified by slight hyperintensity on T_2W images, was also observed at 1 h in both groups (Fig. 2A and I). FA maps for both groups showed fewer changes relative to the other parameters at 1 h after HI injury (Fig. 1D and L). In the severe group, the ADC was high in the striatum at 168 h (Fig. 2O). In the mild group, the low ADC observed in the ipsilateral hemisphere at 1 h was no longer visible at 168 h (Fig. 2G). The hyper- and hypointense regions on DW images in the severe group (Fig. 2N)

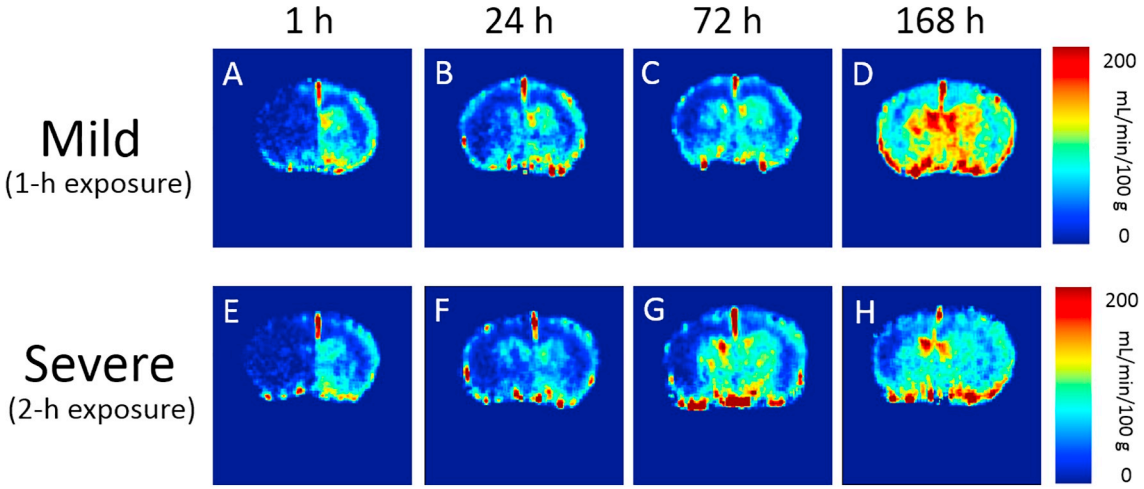

Fig. 1. Representative FAIR images showing the CBF in the mild (A–D) and severe (E–H) groups at 1, 24, 72, and 168 h after HI injury. At 1 h after HI insult, the ipsilateral CBF in both groups declined relative to the contralateral CBF (A, E). The CBF seems to recover at 168 h after HI injury (D, H). CBF, cerebral blood flow; FAIR, flow-sensitive alternating inversion recovery; HI, hypoxic-ischemic.

were consistent with diminished and enhanced signal intensities on ADC maps, respectively (Fig. 2O). At 168 h after the severe HI insult, notable hyperintensities in the ipsilateral hemisphere were observed on T_2W images (Fig. 2M), and FA maps demonstrated low values in the ipsilateral hemisphere (Fig. 2P).

Representative ISO, ICVF, and ODI maps from both groups at 1 and 168 h are shown in Fig. 3. Increased ICVF and ODI in the ipsilateral hemispheres were noticeable in both groups at 1 h after HI injury (Fig. 3B, C, H, and I). The increased values at 1 h seemed to recover at 168 h in the mild group (Fig. 3E and F) but not in the severe group (Fig. 3K and L). In the mild group, the slight hyperintensities on ICVF maps at 168 h (Fig. 3E) resembled the inversed ADC map (Fig. 2G). In the severe group, the injured striatum demonstrated high ISO and ICVF values at 168 h (Fig. 3J and K), and this area was consistent with the

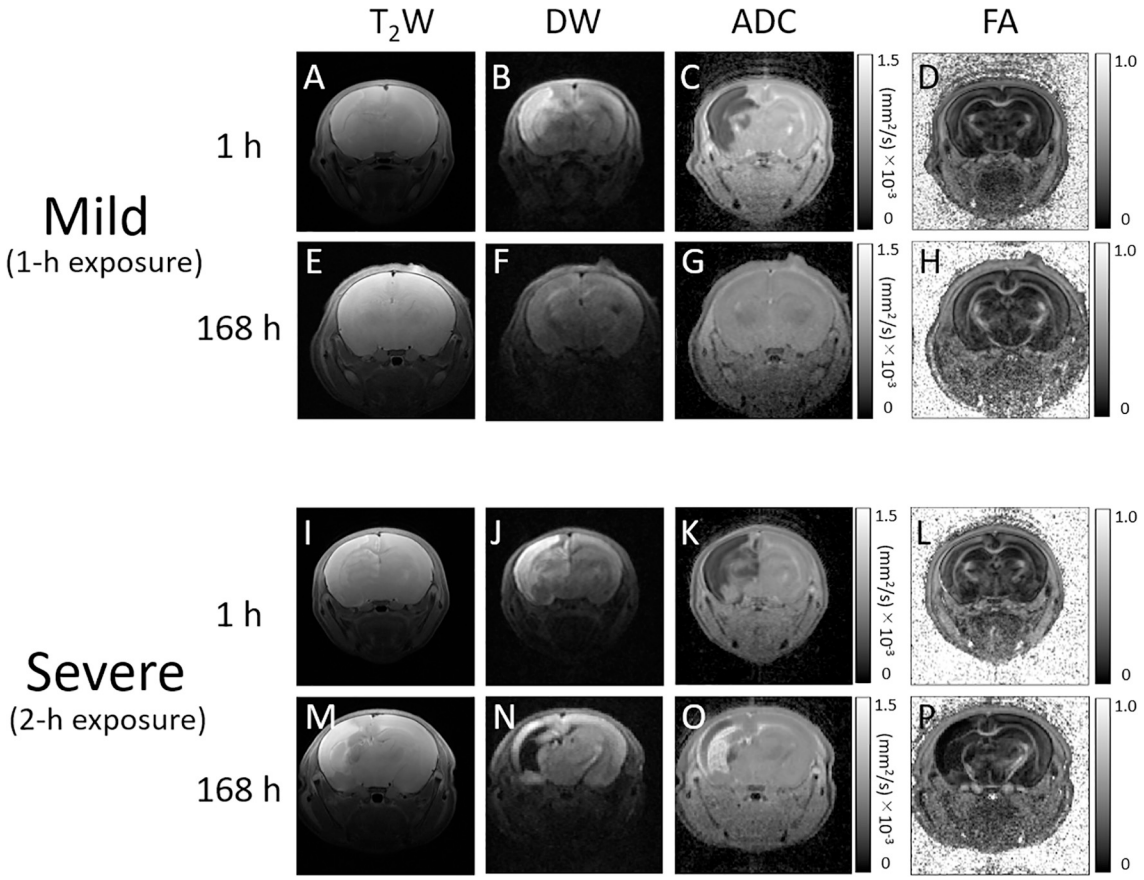

Fig. 2. Representative T_2W images, DW images, FA maps, and ADC maps from the mild (A–H) and severe (I—P) groups at 1 and 168 h after HI injury. The representative images were acquired from different animals than those used in Fig. 1. At 1 h after HI insult, reduced ADC was observed on the ipsilateral vs. contralateral side in both groups (C, K). The severe group showed hyperintensity in the ipsilateral striatum on the ADC map at 168 h (O). ADC, apparent diffusion coefficient; DW, diffusion-weighted; FA, fractional anisotropy; HI, hypoxic-ischemic; T_2W, T_2-weighted.

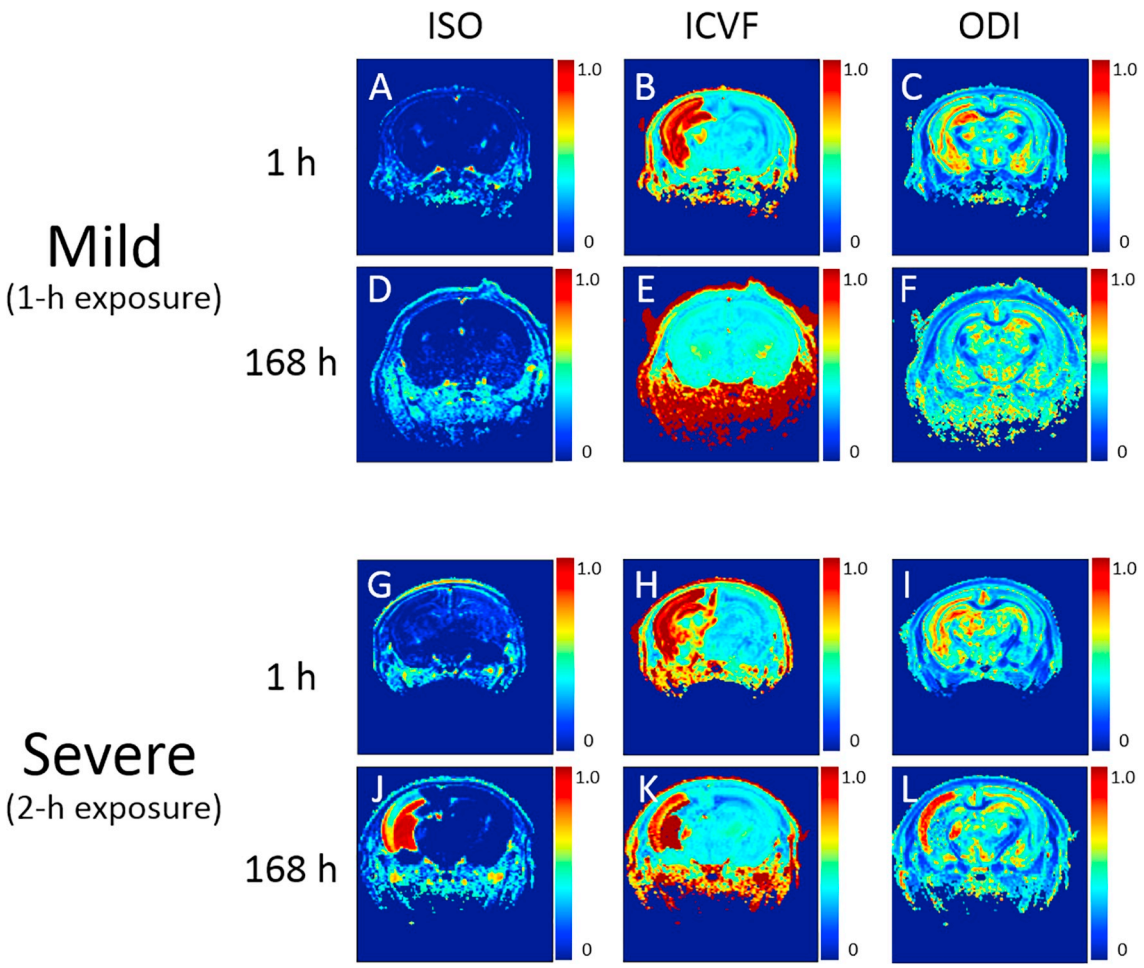

Fig. 3. Representative ISO, ICVF, and ODI maps from the mild (A–F) and severe groups (G–L) at 1 and 168 h after HI injury. The representative images from both groups were obtained from the same animals as those used in Fig. 2. Elevated ICVF and ODI were obvious in both groups at 1 h after injury (B, C, H, I). At 168 h after the severe HI event, ISO and ICVF were elevated within the striatum (J, K). HI, hypoxic-ischemic; ICVF, intracellular volume fraction; ISO, isotropic volume fraction; ODI, orientation dispersion index.

regions of hyperintensity that were observed on the ADC maps (Fig. 2O).

Graphs quantifying the ipsilateral CBF, FA, ADC, ISO, ICVF, and ODI at each time point and in each region in the mild and severe groups are shown in Fig. 4. The CBF and ADC were not significantly different between the mild and severe groups at any of the time points evaluated or within any of the regions examined (Fig. 4A and C). The FA in the severe group was significantly lower than that in the mild group in the cortex and white matter, but not in the striatum, at 168 h, but not at any of the other time points (Fig. 4B). The ISO value in all regions was significantly higher in the mild vs. severe group at 24 h. However, the ISO value was significantly higher in the severe vs. mild group in the striatum at 72 h and in all regions at 168 h (Fig. 4D). The ICVF values in the cortex and striatum at 168 h and in the white matter at 24 and 72 h were significantly higher in the severe group than in the mild group (Fig. 4E). The ODI values at 72 and 168 h in the cortex and at 1 and 72 h in the white matter were significantly higher in the severe group than in the mild group (Fig. 4F).

4. Discussion

In this study, we used NODDI to evaluate and compare different severities of HIE in a rat model at various time points after injury. It has been reported that FA and ADC decrease in infants with serious HIE [11]. Our results revealed that the FA was significantly reduced at 168 h while the ICVF, ISO, and ODI were significantly increased at different points from 1 h and beyond in the severe vs. mild HI insult group. This suggests that NODDI is useful for identifying the severity of the HIE model in the early phase.

Herein, single regions of interest in the cortex, striatum, and white matter were employed because the Rice-Vannucci model, consisting of unilateral common carotid artery ligation with hypoxia, produces a large lesion that includes these regions [17,18]. In the present study, hypoperfusion and/or hyperperfusion tended to be observed within these regions after the severe HI insult. However, as no significant differences in CBF were noted between the two groups, this suggests that the local CBF did not contribute to the variations in severity. Hence, CBF likely aided in activating the metabolite response including the disrupted delivery of oxygen and glucose and secondary energy failure rather than expanding the injury.

Previously, Qiao et al. [19] demonstrated that both white matter and gray matter are damaged following moderate (90 min at 35.5 °C) but not mild (45–50 min at 34.5 °C) HI insult. Moreover, Meng et al. [18] reported that white matter is more easily injured than is gray matter in HIE, though ADC maps and T_2W images could not distinguish such differential susceptibility. In the present study, the only indicator capable of identifying a significant difference between the severe and mild groups at 1 h was the ODI within the white matter (elevated in the severe vs. mild group). This result supports that NODDI metrics can be used to evaluate the severity and regional susceptibility in HIE. Increased ODI on the ipsilateral side has also been observed in patients with stroke [20,21]. It is known that the ODI represents the dispersion

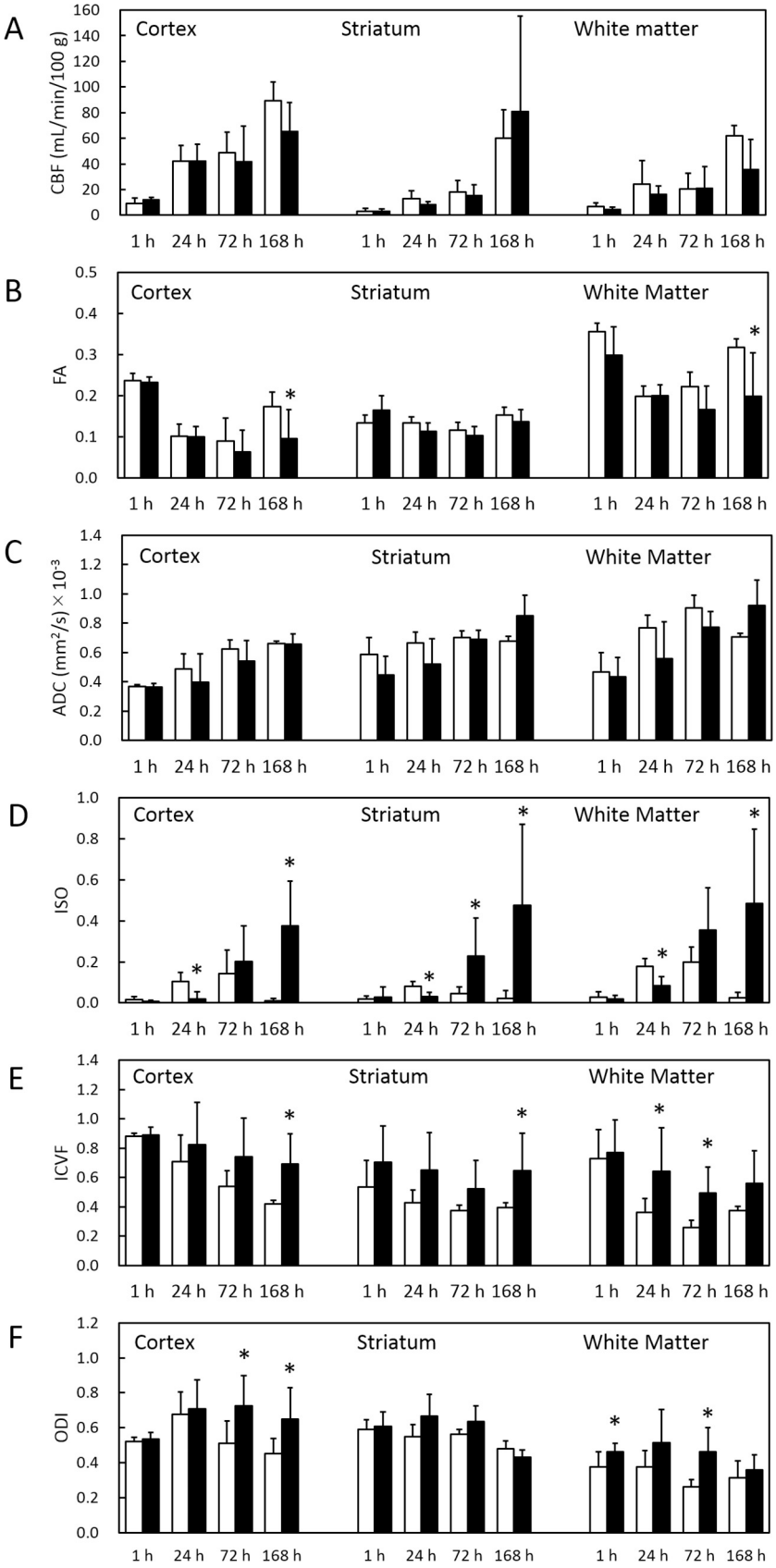

Fig. 4. Graphs quantifying the ipsilateral CBF (A), FA (B), ADC (C), ISO (D), ICVF (E), and ODI (F) in the mild (white bars, $n = 6$) and severe (black bars, $n = 7$) groups in each region at each time point. *$P < 0.05$. ADC, apparent diffusion coefficient; CBF, cerebral blood flow; DW, diffusion-weighted; FA, fractional anisotropy; HI, hypoxic-ischemic; ICVF, intracellular volume fraction; ISO, isotropic volume fraction; ODI, orientation dispersion index.

of nonparallel axons around a central orientation based on a cylindrically symmetric Watson distribution [13,21]. Therefore, the elevated ODI values we identified in the severe vs. mild group indicate that the severe HI injury induced the loss of the myelin sheath and disorder of the white matter microstructure to a greater degree than did the mild HI injury. These findings demonstrate that the ODI is the optimal parameter for revealing the state of HIE and imply that it may contribute to the ipsilateral reduction in FA.

Significant increases in ICVF and ISO were observed in both groups, and we visually confirmed the presence of reduced ADC in the ipsilateral hemispheres of both groups. Research has shown that the ADC is reduced in the acute phase of HIE because of cell swelling and a decreased extracellular space, i.e., cytotoxic edema [22]. Further, 1-h exposure to hypoxia is associated with mild cerebral edema, which recovers entirely by 72 h [23]. Here, the ipsilateral ISO in the mild group was significantly higher than that in the severe group at 24 h (all regions). Subsequently, the ipsilateral ISO in the mild group returned to a level that was similar to the contralateral ISO level at 168 h (Fig. S1G). Thus, the temporal ISO elevations and ADC reductions that were observed in the mild group are likely related to temporal cell swelling. Thereafter, ADC recovers and exhibits higher values than those of normal tissues due to water inflow from vessels to cerebral tissue [22,24]. Late injury of the striatum was demonstrated by enhanced ADC in the severe group, and this finding was consistent with the observed hyperintensity regions on ICVF and ISO maps. The delayed appearance of hyperintensities on ISO maps in the severe group is probably related to elevated water diffusion in vasogenic edema due to disruption of the blood brain barrier because the ISO parameter represents the changes in free-water diffusion compartments [19]. On the other hand, the enhanced ICVF represents increases in neurite density, which contradicts the advanced stage of HIE. Wang et al. [21] reported that high ICVF values in the ischemic region should be interpreted not as neurite density but as alterations in the relative volume of the intracellular compartments.

One limitation of our study was related to the animal model we used. In this study, some animals had varying degrees of cerebral damage, despite being subjected to similar levels of hypoxia (1 or 2 h to induce mild or severe impairment). We selected the above values because exposure to hypoxia for $\geq$90 min results in extensive axonal damage and neuronal loss [19,22]. Furthermore, we selected our HIE model based on the fact that the animals exhibit lesions on DW images at an early stage, a characteristic that is observed in both animal models of HIE [17,25] and humans with HIE [26–28]. We think it is also important to note a discrepancy between our NODDI findings and those of previous studies. Specifically, the elevated ISO we observed in the ipsilateral hemispheres of both groups did not correspond with the findings of studies examining patients with stroke [20,21]. Therefore, caution should be exercised when trying to use NODDI to evaluate diseased brains, especially since it was originally patterned on healthy tissues in the human brain.

In conclusion, the present study demonstrated that NODDI can be used to determine the severity of HIE in neonatal rats. In particular, employing the ODI in the early phase revealed clear differences between the mild and severe HI injuries. Our results suggest that NODDI, especially the ODI, has the potential to assist in the accurate diagnosis and treatment of HIE.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mri.2019.07.013.

Declaration of Competing Interest

None of the authors has any conflicts of interest to report.

Acknowledgements

This work was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI [grant number 19K08172] and Agency for Medical Research and Development (AMED) [grant number JP19dm0307026].

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