Dynamics of Rabbit Brain Edema in Focal Lesion and Perilesion Area after Traumatic Brain Injury: A MRI Study

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Abstract

To understand the dynamics of brain edema in different areas after traumatic brain injury (TBI) in rabbit, we used dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and diffusion-weighted imaging (DWI) to monitor blood–brain barrier (BBB) permeability and cytotoxic brain edema after weight drop-induced TBI in rabbit. The dynamics of BBB permeability and brain edema were quantified using K^{trans} and apparent diffusion coefficient (ADC) in the focal and perifocal lesion areas, as well as the area contralateral to the lesion. In the focal lesion area, K^{trans} began to increase at 3 h post-TBI, peaked at 3 days, and decreased gradually while remaining higher than sham injury animals at 7 and 30 days. ADC was more variable, increased slightly at 3 h, decreased to its lowest value at 7 days, then increased to a peak at 30 days. In the perifocal lesion area, K^{trans} began to increase at 1 day, peaked at 3–7 days, and returned to control level by 30 days. ADC showed a trend to increase at 1 day, followed by a continuous increase thereafter. In the contralateral area, no changes in K^{trans} and ADC were observed at any time-point. These data demonstrate that different types of brain edema predominate in the focal and perifocal lesion areas. Specifically cytotoxic edema was predominant in the focal lesion area while vasogenic edema predominated in the perifocal area in acute phase. Furthermore, secondary opening of the BBB after TBI may appear if secondary injury is not controlled. BBB damage may be a driving force for cytotoxic brain edema and could be a new target for TBI intervention.

Key words: blood-brain barrier; cytotoxic edema; diffusion-weighted imaging; dynamic contrast-enhanced MRI; rabbit; traumatic brain injury; vasogenic edema

Introduction

IN WESTERN COUNTRIES, traumatic brain injury (TBI) has an incidence of 0.235% and is a major cause of morbidity and mortality in young people (León-Carrión et al., 2005; Tagliaferri et al., 2006). TBI consists of two stages of pathophysiological injury: primary (e.g., brain contusion, parenchyma hemorrhage, subarachnoid hemorrhage, and diffuse axonal injury [DAI]) and secondary (e.g., edema, herniation, ischemia, and infarction) (Le and Gean, 2009). Traumatic brain edema, which is a secondary injury, could induce a series of events, including intracranial hypertension and reduced blood flow and volume, which in turn aggravate neuronal swelling and cause dysfunction (Shlosberg et al., 2010). Therefore, effective clinical treatment requires ongoing monitoring of the status of edema after TBI.

Traumatic brain edema can be classified into two main types: vasogenic (e.g., blood–brain barrier [BBB] opening) and cytotoxic. Vasogenic edema is one of the driving forces of

cytotoxic brain edema (Donkin et al., 2010; Habgood et al., 2007), which is the dominant type observed after TBI (Unterberg et al., 2004). Whether a secondary opening of the BBB occurs remains controversial (Başkaya et al., 1997; Donkin et al., 2010; Shlosberg et al., 2010); the impaired function of BBB might affect the course of long-term TBI complications, including cognitive and psychological impairments, apparent diffusion (AD), and seizures (Ruttan et al., 2008; Zlokovic, 2008). Therefore, to provide targeted treatment for brain swelling, the dynamics of brain edema after TBI must be elucidated.

Methods that are currently available to evaluate BBB integrity include semi-quantitative analysis of Evans Blue (Lahoud-Rahme et al., 2009; Qu et al., 2009), quantitative detection of cerebrospinal fluid–serum albumin index (CSF-AI) (Song et al., 2010), histology (Lescot et al., 2010), and MRI (Cohen et al., 2009; Sourbron et al., 2009). Of these techniques, only MRI allows for repeated sampling within the same subjects over time in a non-invasive manner. Dynamic

contrast-enhanced MRI (DCE-MRI) and its volume transfer coefficient (K^{trans}) can be used to quantitatively analyze BBB permeability (Abo-Ramadan et al., 2009; Haris et al., 2008; Song et al., 2010) and has been applied widely to monitor tumor angiogenesis (Ferrier et al., 2007; Turkbey et al., 2009). Conversely, diffusion-weighted imaging (DWI), a sensitive modality in the early detection of cytotoxic brain edema, which could be used as a tool to distinguish between cytotoxic and vasogenic edema (Barzó et al., 1997; Marmarou et al., 2000). The aim of this study was to use DCE-MRI combined with DWI to investigate the sequelae of TBI-induced brain edema, including changes in BBB permeability and cytotoxic edema and their relationship.

Methods

Animal model

This study was approved by the institutional animal research committee and was conducted in accordance with the guidelines of the International Council on Animal Care. A total of 21 New Zealand white rabbits (3–4 month old), weighing 2.5–3 kg, were randomly assigned to TBI ($n=15$) or sham injury ($n=6$). The traumatic brain injury was induced by using a modified weight-drop device adapted from Bieganski and associates (Bieganski et al., 2004). Specifically, rabbit was anesthetized with 2.5% pentobarbital sodium (1 mL/kg) via the ear vein, and then placed into a stereotaxic apparatus with the head fixed. The skull was exposed, and a circular craniectomy (1 cm in diameter) was created with a dental drill on the right convexity between bregma and lambda (anterior edge 3 mm posterior to bregma; lateral edge 2 mm medial to the left lateral ridge), leaving the dura intact. At 24 h after the operation, the rabbit head was held in a stereotaxic apparatus and a 60 g weight was dropped from a height of 20 cm, resulting in a focal injury to the right hemisphere. After trauma, the rabbit received supporting oxygenation with 95% oxygen for up to 2 min. The sham injury group underwent surgery, but received no TBI.

MRI protocols

All rabbits underwent MRI at 3 h and 1, 3, 7, and 30 days after TBI or sham injury using a clinical 3.0 T MRI scanner (Intera-achieva SMI-2. 1, Philips Medical System, Best, Netherlands) and 8-channel head coil. The MRI parameters for the T2-weighted image (T2W) were: TR/TE=1600/100 msec, NSA=6, slice thickness=2 mm, FOV=100×100 mm and matrix=200×192. The parameters for the pre-T1-weighted image (T1W) were: TR/TE=500/20 msec, NSA=6, slice thickness=2 mm, FOV=100×100 mm and matrix=224×270. DWI was acquired in the axial plane by using a single-shot EPI spin echo sequence (TR 1128/TE 75 msec/NSA 4/3 mm thickness/FOV 100×100 mm/matrix 92×90). Two b values (0.600 sec/mm²) were applied along three gradients coinciding with major physical axes (x , y , and z) and subsequently MD maps were automatically generated at the console. The post-T1W images were performed with the same parameters as the one used for the pre-T1W images. The parameters for the 3D-THRIVE sequence used in DCE-MRI were: TR/TE=6.8/3.2 msec. Before the DCE-MRI scans, the 3D-THRIVE sequence with FA (flip angle)=4° was scanned for one phase. Then the THRIVE sequence was scanned

dynamically for 30 phases for DCE-MRI. The 4° and 8° flip angles and the same TR/TE were used to generate the T1 maps. During the DCE-MRI scanning, after the pre-contrast baseline scans, 0.1 mmol/kg Gd-DTPA (0.5 mol/L Magnevist; Bayer HealthCare Pharmaceuticals, Guangzhou, Guangdong, China) was injected through the ear vein at a constant rate of 0.2 mL/kg/min over 1 min. After the injection of Gd-DTPA, 2-min saline was infused, using a syringe connected to polyethylene microtubing, driven by a microinfusion pump (Gene & I Scientific Ltd., Beijing, China). Thirty DCE-MRI 3D-THRIVE sequences were obtained over 7.5 min at a temporal resolution of 15 sec/vol. The total scan time of all sequences was about 30 min.

Data processing

All pre-contrast and dynamic post-contrast THRIVE images were transferred to IDL-based permeability image processing software (CineTool, GE Healthcare, Waukesha, WI). The middle cerebral artery was selected as the input artery. The permeability parameter K^{trans} was calculated based on the two-compartment model of modified Tofts (Tofts et al., 1991, 1999). This kinetic model assumes that the total concentration of contrast agent in a tissue is determined by the concentrations in two compartments: the intravascular space and the extravascular extracellular space. Other compartments are assumed to take up no contrast agent.

In this model, K^{trans} was considered for Gd-DTPA influx from the intravascular space into the extravascular extracellular space. The K^{trans} and ADC were calculated by manually outlining the regions of interest (ROIs). Three ROIs at all time-points were manually drawn in a 2 mm single slice T2WI, as shown in Figure 1. ROIs for the TBI group included the focal and perifocal lesion areas, as well as the contralateral area. The focal lesion area refers to the lesioned area that was outlined based on hyperintensity in T2 weighted images and using the signal intensity difference

FIG. 1. ROIs drawn on a T2WI at 3 days post-injury showing the location of focal lesion (F), perifocal area (P), and contralateral area (C).

(difference threshold was 300) of T2W to detect the limit between hyperintense and healthy appearing tissue. Perifocal lesion area refers to the ipsilateral parietal area excluding the focal lesion and including tissue that appears normal in T2 weighted images. In addition, we assessed the contralateral area that corresponded with the focal lesion and perifocal lesion area. During the calculation of these two variables on different ROIs, we tried to avoid the hemorrhage area located at the ROIs to exclude its influence. The ROI for the sham injury group was the area that corresponded to the contralateral area in the TBI group. All of the above process was performed by two radiologists, respectively. Thereafter the average value of K^{trans} or ADC between these two radiologists were used.

Statistical analysis

SPSS for Windows software (version 16.0; Chicago, IL) was used for statistical analysis with $p < 0.05$ considered significant. Values are presented as mean $\pm$ standard deviation (SD). Differences between TBI and sham injury groups were calculated using Kruskal-Wallis followed by post hoc analysis with Mann-Whitney U tests. Differences between time-points were calculated using Friedman followed by post hoc analysis with Wilcoxon tests. Correlations between various parameters were calculated using the Spearman correlation test.

Results

Final sample

Of the 15 rabbits in the TBI group, three were excluded due to mortality after excessive anesthesia and injury ($n=2$) or motion artifacts ($n=1$). All six rabbits in the sham injury group were included. In the 12 TBI rabbits, BBB damage and brain edema were observed in the post-T1W, T2W, and DWI (Fig. 2).

Changes in K^{trans}

In the focal lesion area, TBI animals showed an immediate and sustained increase in K^{trans} post-injury compared to

sham animals. Specifically, K^{trans} (min^{-1}) was increased by 0.023 at 3 h, 0.027 at 1 day, 0.05 at 3 days, 0.024 at 7 days, and 0.009 at 30 days ($p \leq 0.001$) (Fig. 3A). Also K^{trans} values were different between some adjacent two time-points ($p < 0.01$ between 1 and 3 days, 3 and 7 days, and 7 and 30 days). So it was clearly noted that beginning at 3 days K^{trans} began to decline ($p < 0.01$), though it remained elevated over sham levels.

In the perifocal lesion area, TBI showed a delayed and transient increase in K^{trans} compared to sham animals (Fig. 3B). Specifically, K^{trans} was no different than sham levels at 3 h. It increased by 0.013, 0.028, and 0.024 ($p \leq 0.001$) at 1, 3, and 7 days, respectively, and returned to sham levels by 30 days. Also we found that K^{trans} values were different between some adjacent two time-points ($p < 0.01$ between 3 h and 1 day, 1 and 3 days, and 7 and 30 days).

In the contralateral region, unlike in the focal and perifocal lesion areas, K^{trans} was not affected. No significant differences were observed between TBI and sham injury or between different time-points (Fig. 3C).

Changes in ADC

In the focal lesion area, TBI animals demonstrated time-dependent changes in ADC values compared to sham injury animals (Fig. 4A). Specifically, ADC increased by 11% ($p \leq 0.001$) at 3 h, returned to sham level by 1 day, and then decreased by 25% and 40% ($p \leq 0.001$) to below sham level at 3 and 7 days, respectively. By 30 days, ADC showed a dramatic 90% increase ($p \leq 0.001$) compared to sham animals. The ADC values were different ($p < 0.01$) between all adjacent two time-points. This pattern suggests that ADC values decreased obviously due to cytotoxic edema after an initial increase at 3 h. With the development of the injured tissue, the neuron collapsed and the lesion liquefied, which increased the extent of Brownian motion of water molecules, so the ADC values increased dramatically at 30 days. In the perifocal area, ADC also showed time-dependent changes, which were delayed and more transient than in the focal area (Fig. 4B). At 3 h, ADC was similar to that of sham animals. By day 1, ADC had increased relative to 3 h ($p < 0.01$) and showed a

FIG. 2. MRIs from a representative animal at different time-points. T2-WI and DWI show the focal lesion, while post-contrast T1-WI (post-T1-WI) show Gd-DTPA enhancement in the focal lesion area.

FIG. 3. K^{trans} in different brain areas over time after TBI. (A) In the focal lesion area, K^{trans} were higher in the TBI group than in sham group at all time-points with the peak at day 3. (B) In the perifocal area, K^{trans} were higher in the TBI group than the sham group at 1, 3, and 7 days with the peak from days 3–7. (C) In the contralateral area, K^{trans} was similar in the TBI and sham groups at all time-points. Data represent mean $\pm$ SD. * $p < 0.01$ as compared to the sham group by Kruskal-Wallis with Mann-Whitney post hoc test.

FIG. 4. ADC in different brain areas over time after TBI. (A) In the focal lesion area, ADC increased at 3 h in the TBI group compared to the sham group, followed by a decrease that was lowest at 7 days, then an increase through 30 days. (B) In the perifocal area, ADC showed a trend to increase at day 1 with a continuous increase thereafter. (C) In the contralateral area, ADC was similar in the TBI and sham groups at all time-points. Data represent mean $\pm$ SD. * $p < 0.01$ as compared to sham group by Kruskal-Wallis with Mann-Whitney post hoc test.

trend to be increased relative to sham animals ($p=0.075$). ADC increased by 2%, 3%, and 6% ($p<0.01$) at 3, 7, and 30 days, respectively. The ADC values were different ($p<0.05$) between all adjacent time-points. In the contralateral area, similar to K^{trans} , ADC was not affected. No significant differences were observed between TBI and sham injury or between different time-points (Fig. 4C).

Correlations between variables

No significant correlations were observed in K^{trans} or ADC between focal lesion and perifocal area at any time-point. Specifically, the correlation between focal lesion and perifocal area in K^{trans} on different time-points was $r = -0.286$, $p = 0.386$ at 3 h; $r = -0.248$, $p = 0.437$ at 1 day; $r = 0.362$, $p = 0.247$ at 3 days; $r = -0.056$, $p = 0.862$ at 7 days; and $r = 0.369$, $p = 0.237$ at 30 days, respectively. The correlation of ADC was $r = -0.286$, $p = 0.386$ at 3 h; $r = -0.191$, $p = 0.552$ at 1 day; $r = -0.340$, $p = 0.279$ at 3 days; $r = -0.380$, $p = 0.224$ at 7 days; and $r = 0.161$, $p = 0.618$ at 30 days, respectively. Similarly, no significant correlations were observed between K^{trans} and ADC in the focal or perifocal lesion area at any time-point, but we see a trend to be correlated at 3 days in the perifocal lesion area. Specifically, in the focal lesion area, the correlation between K^{trans} and ADC on different time-points was $r = 0.018$, $p = 0.957$ at 3 h; $r = 0.464$, $p = 0.129$ at day 1; $r = -0.308$, $p = 0.331$ at 3 days; $r = -0.462$, $p = 0.130$ at 7 days; and $r = -0.131$, $p = 0.686$ at 30 days, respectively. In the perifocal lesion area, the correlation on different time-points was $r = -0.51$, $p = 0.09$ at 3 h; $r = 0.285$, $p = 0.370$ at day 1, $r = 0.561$, $p = 0.058$ at 3 days; $r = 0.320$, $p = 0.310$ at 7 days; and $r = 0.056$, $p = 0.862$ at 30 days, respectively.

Discussion

As traumatic edema is an important factor in clinical prognosis, it is imperative to elucidate the dynamics of edema after TBI.

Dynamics of BBB permeability

Secondary opening of BBB at the focal lesion site. TBI-induced opening of the BBB can be primary or secondary. The traditional view is that primary opening occurs immediately after TBI, peaks at 4–6 h, and resolves within 7 days. Whether secondary opening occurs remains controversial (Başkaya et al., 1997; Donkin et al., 2010; Habgood et al., 2007). The current study found that BBB opening occurred immediately after TBI and peaked at 3 days. However, the BBB did not close completely within 7 days; it remained open even at 30 days after TBI. It showed that the time to peak was delayed and that the course of BBB opening was prolonged compared to the primary opening.

These results support the existence of secondary opening and furthermore suggest that primary and secondary opening coexists in the acute phase after TBI. TBI itself could cause damage to neurons and blood vessels, inducing neuroinflammation and releasing inflammatory mediators (e.g., metalloproteases and vasoactive agents) in acute phase to increase the BBB permeability (Abbott et al., 2000; Hayashi et al., 2009). Without secondary injury, the neuroinflammation and inflammatory mediators may diminish and BBB closing may occur within 7 days, consistent with the tradi-

tional view of primary opening (Shlosberg et al., 2010). However, secondary injury, such as intracranial hypertension and decreased regional cerebral blood flow (rCBF) and blood volume (CBV) commonly appear after TBI (Le and Gean, 2009). These factors could exacerbate the extent and duration of BBB opening by causing tissue hypoxia, which would aggravate neuroinflammation and release inflammatory mediators (Gröger et al., 2005). Neuroinflammatory processes are now known to accompany many brain pathologies, including TBI [Infante-Duarte et al., 2008; Oby and Janigro, 2006; Skaper, 2007]. Moreover, the neuroinflammatory response in patients with TBI begins within hours after injury and lasts up to several weeks [Morgenti-Kossmann et al., 2007]. Therefore, we believe that secondary BBB opening occurs when intracranial hypertension, decreased rCBF or CBV, or neuroinflammation exist. To rapidly repair the damaged BBB, we suggest that it is important to reduce intracranial pressure, improve rCBF and CBV, and relieve inflammation.

BBB opening in the perifocal lesion area. Previous research has demonstrated that the perifocal lesion area may also show a series of pathophysiological changes after TBI. Immonen and associates (2009) found a transient vasogenic edema in the perifocal area from 3 h to 9 days after injury. Consistent with this study, the current study showed that the BBB began to open in the perifocal area by day 1 after TBI, peaking at 3–7 days and closing within 30 days. In addition to changes in the acute phase, Immonen and colleagues (2009) found that MRI parameters (diffusion [Dav], T2 and T1 ρ relaxation times [T2, and T1 ρ]) returned to normal, then increased again in the subacute phase, which they interpreted to be a result of neurodegeneration, DAI, and chronic inflammation. In the current study, we did not observe a second BBB opening in the perifocal area during the subacute phase. It is possible that the factors that increased the MRI parameters (neurodegeneration, DAI, and chronic inflammation) in the previous study imposed only an minor influence on BBB, which would typically open due to angiogenesis, which is predominant in the acute phase, declining thereafter in perifocal lesion area (Nag, 2002). Thus, the BBB reached peak opening in the perifocal area within 7 days and closed in the subacute phase. The lack of correlation between perifocal and focal lesion areas may indicate that BBB permeability in the perifocal area did not depend on the extent of the primary focal lesion.

Lack of BBB changes in the contralateral area. We did not find any BBB changes in the contralateral area. A previous study showed BBB changes in the contralateral hippocampus similar to those observed in the perifocal area (Immonen et al., 2009). This may be due to the fluid-percussion device used in their model, which can induce a wider injury area compared to that of our weight drop device (Cernak, 2005).

Evolution of cytotoxic edema

Cytotoxic brain edema is predominant in the focal lesion area. The current view is that cytotoxic edema is the predominant type of edema in TBI patients (Donkin et al., 2010; Unterberg et al., 2004). Our data support this view. ADC values increased by about 11% in the focal lesion area at 3 h after TBI, followed by a return to normal levels at 1 day, then a 40% decrease at 7 days and 90% increase at 30 days compared

to the sham group. The increased ADC values at 3 h indicate that the vasogenic edema was predominant at this time, as this could drive more water from the vasculature into the extracellular extravascular space to induce high ADC values. Subsequently, brain ischemia and hypoxia would deteriorate due to brain swelling and intracranial hypertension, which would cause neuron dysfunction and further aggravate the cytotoxic brain edema. At this time, cytotoxic brain edema would predominate, and extracellular extravascular space was to be decreased, leading to reduced ADC values that reached their lowest values at 7 days. Finally, cytotoxic edema would diminish due to the neuron necrosis and cell collapse, leading to increased ADC by 30 days. Therefore, our data support the co-existence of cytotoxic and vasogenic edema in the focal area within the first week after injury, with cytotoxic edema predominating in the acute phase.

Predominance of vasogenic edema in perifocal area. ADC values showed a trend to rise at day 1 and were significantly higher from day 3 until the end of the study, reaching a peak increase of 6% by day 30. This indicates that vasogenic edema was dominant in the perifocal area. In contrast to the previous study (Immonen et al., 2009), we did not find a decrease in D_{av} at 3 h, possibly because only a small number of the cells were affected in the perifocal area (Cortez et al., 1989). In fact, in contrast to the focal lesion, the decrease in the previous study on D_{av} values at perifocal area was only 7% at 3 h. We suggest that ADC values may have been higher in the TBI group than in the sham group due to the vasogenic edema observed in the acute phase and neurodegeneration, DAI, and chronic inflammation observed in the subacute phase (Immonen et al., 2009). As with K^{trans} , no correlation between focal and perifocal lesion areas was observed for ADC. Thus, we can conclude that the extent of TBI-induced injury in the perifocal area did not depend on the extent of the primary focal lesion.

Lack of ADC changes in the contralateral area. Similar to K^{trans} , no ADC changes were observed in the contralateral area, possibly due to a smaller area of injury caused by the weight drop device (Cernak, 2005).

Relationship between vasogenic and cytotoxic edema. During the acute phase of TBI, cytotoxic brain edema predominates and can lead to neuronal dysfunction. Neurons transition into apoptosis and eventually necrosis if the pathological changes continue without effective treatment. However, cytotoxic edema alone is not enough to aggravate the lesion because water content is not increased. When BBB opening occurs, water is driven from the vessels into the extracellular extravascular space and then enters the cells (Beaumont et al., 2000). Although we did not find a correlation between K^{trans} and ADC, BBB permeability is high and ADC values decline dramatically during the acute phase. The absence of correlation may be due to the small sample size as well as a lack of synchronization of the start and end time of BBB opening with cytotoxic edema. Thus, the BBB may be a target for treatments to relieve brain edema and swelling.

Limitations

One limitation of this study was the relatively short (30-day) time span. According to an 11-month study, MRI parameters showed a series of changes at acute, subacute, and chronic phases. However, we found that necrosis and liquefaction of the majority of cells in the focal lesion area occurred by 30 days post-TBI, suggesting that most parameters may not change after 30 days with the exception of ADC. A second limitation is the absence of a gold standard for BBB permeability. However, DCE-MRI and its volume transfer coefficient (K^{trans}) have been widely used in clinical and animal experiments, and K^{trans} has been confirmed as a good surrogate marker of BBB permeability, especially in the T-K model (Cao et al., 2009; Haris et al., 2008; Tofts et al., 1991, 1999). Also, the K^{trans} map in our study displayed the BBB disruption clearly (Fig. 5).

Conclusion

Our results showed that the types of edema observed in the focal and perifocal lesion areas were different and that cytotoxic edema was predominant in the focal lesion area and vasogenic edema in perifocal area in acute phase. Furthermore, our data suggest that secondary opening of the BBB may occur after TBI if secondary injury occurred. Although

FIG. 5. (A) Quantitative analysis of a representative animal brain DCE-MRI on processing software (CineTool) 3 days after TBI. The lighter line represents the focal lesion area and the darker line indicates the middle cerebral artery. (B) K^{trans} map of the same animal. It is clear that BBB permeability increased significantly at the focal lesion area.

we did not find a correlation between K^{trans} and ADC at any time-point, BBB damage may be a driving force for cytotoxic brain edema and could be a treatment target for TBI.

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Author Disclosure Statement

The authors have no financial interests to disclose.

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