Decreased apparent diffusion coefficient in the pituitary and correlation with hypopituitarism in patients with traumatic brain injury

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OBJECT The relationship between microstructural abnormality in patients with traumatic brain injury (TBI) and hormone-secreting status remains unknown. In this study, the authors aimed to identify the role of the apparent diffusion coefficient (ADC) using a diffusion-weighted imaging (DWI) technique and to evaluate the association of such changes with hypopituitarism in patients with TBI.

METHODS Diffusion-weighted images were obtained in 164 consecutive patients with TBI within 2 weeks after injury to generate the pituitary ADC as a measure of microstructural change. Patients with TBI were further grouped into those with and those without hypopituitarism based on the secretion status of pituitary hormones at 6 months postinjury. Thirty healthy individuals were enrolled in the study and underwent MRI examinations for comparison. Mean ADC values were compared between this control group, the patients with TBI and hypopituitarism, and the patients with TBI without hypopituitarism; correlational studies were also performed. Neurological outcome was assessed with the Glasgow Outcome Scale (GOS) for all TBI patients 6 months postinjury.

RESULTS In the TBI group, 84 patients had hypopituitarism and 80 had normal pituitary function. The pituitary ADC in TBI patients was significantly less than that in controls (1.83 ± 0.16 vs 4.13 ± 0.33, p < 0.01). Furthermore, the mean ADC was much lower in TBI patients with hypopituitarism than in those without pituitary dysfunction (1.32 ± 0.09 vs 2.28 ± 0.17, p < 0.05). There was also a significant difference in ADC values between patients with hyperprolactinemia and those with normal prolactin levels (p < 0.05). Additionally, the receiver operating characteristic curve analysis showed that the pituitary ADC could predict hypopituitarism with a sensitivity of 90.0% and a specificity of 90.1% at the level of 1.720 (ADC value). Finally, the ADC value was positively correlated with neurological outcome at 6 months following TBI (r = 0.602, p < 0.05).

CONCLUSIONS Use of DWI demonstrated that the pituitary ADC is correlated with hormone-secreting status in TBI patients. The authors suggest that pituitary ADC may be a useful biomarker to predict pituitary function in patients with TBI.


KEY WORDS apparent diffusion coefficient; diffusion-weighted imaging; traumatic brain injury; hypopituitarism
and behavioral symptoms in this population. However, direct anatomical evidence of hypopituitarism after TBI is extremely difficult to detect with conventional imaging techniques. Recent technical developments in MRI, such as diffusion-weighted imaging (DWI), have enabled early and noninvasive detection of microstructural brain damage. Using DWI, pituitary infarction may be diagnosed by the presence of restricted water diffusion. Nevertheless, the relationship between these characteristics in the pituitary and the hormone-secretion status of patients, especially TBI patients, remains unknown.

In the present study, we calculated the mean apparent diffusion coefficient (ADC) values in our assessment of pituitary microstructure and examined the role of ADC in predicting the prognosis of pituitary function and its value in differentiating TBI patients with different levels of secretory function.

Methods

We prospectively enrolled 169 TBI patients between July 2011 and April 2013 at Shanghai Pudong New Area People’s Hospital. We excluded 5 patients with microadenomas and/or empty sella turcica from our study to avoid the partial volume effect on the measurement of regions of interest (ROIs). Consequently, our TBI study population consisted of 164 patients (90 men and 74 women) with a mean age of 48 years (range 23–73 years). Thirty age- and sex-matched healthy controls (average age 49 years, range 18–59 years) were also enrolled in the study and underwent imaging for comparison. The study protocol was approved by our institutional review board, and written patient consent was obtained from patients’ relatives before enrollment into the study. We excluded TBI patients with hormone replacement before and after brain insults and those patients with diabetes mellitus and other endocrine diseases.

MRI Sequences and Image Processing

For the MRI study, we used our hospital protocol and a 1.5-T superconducting scanner (GE Medical Systems). Coronal T1-weighted images were acquired as inversion recovery prepared sequences. The parameters were as follows: TR 2500 msec, TE 16 msec, FOV 18 × 18 cm, matrix size 256 × 192, slice thickness 3 mm, interslice gap 0.3, and 1 acquisition. For coronal T2-weighted images, the parameters were: TR 4000 msec, TE 130 msec, FOV 18 × 18 cm, matrix size 448 × 224, slice thickness 3 mm, interslice gap 0.3, and 1 acquisition. Sagittal DWI was performed with a b value of 1000, TR 6000 msec, TE 125 msec, FOV 22 × 22 cm, matrix size 128 × 128, slice thickness 4 mm, and an interslice gap of 0.3.

A single author (B.H.) performed the ROI analyses using dTV software (University of Tokyo) and was blinded to laboratory data and patient group (control vs TBI). A manually drawn ROI was positioned in the pituitary on the sagittal diffusion-weighted image (Fig. 1). For all cases and controls, the ADC measurements were computed in 6 serial images within the pituitary. Mean ADC values were calculated in these ROIs by means of Volume-One software (University of Tokyo).

Clinical Data

All patients in the TBI group underwent a hormone test 6 months postinjury at the outpatient department. Clinical data, including the patient’s age, sex, time of MRI scan from injury, initial Glasgow Coma Scale (GCS) score, and 6-month Glasgow Outcome Scale (GOS) score were recorded.

Serum Sample Collection

Blood was collected at 7:00–7:30 AM from TBI patients. Upon collection, each sample was centrifuged, aliquoted in polypropylene cryovials, and stored at −80°C until the time of assay. No blood tests were performed in the control group.

Serum Hormone Measurements

Hypopituitarism was defined as the presence of single or multiple pituitary axis deficiencies. Increased prolactin secretion was defined by a serum prolactin level > 396 mIU/L (22 ng/ml) regardless of age. A gonadotropin deficiency was defined for women as secondary amenorrhea or a menstrual disorder with a blood estradiol level below 20 pg/ml and normal or low gonadotropin levels and for men as a blood testosterone level below 8.5 nmol/L with normal or low gonadotropin levels. Thyrotropin deficiency was defined as a low free thyroxine (T4) or free triiodothyronine (T3) level with normal or low thyroid-stimulating hormone (TSH) levels. Corticotropin deficiency was defined as a blood cortisol level below 138 µg/dl. Growth hormone (GH) deficiency was defined as a growth hormone level < 5 ng/ml on direct testing. Both GH and corticotropin tests were based upon the insulin tolerance test.
Neurological Outcome

Neurological outcome was evaluated with GOS scores at 6 months postinjury, with a score of 5 indicating a good recovery, 4 indicating moderate disability, 3 indicating severe disability, 2 indicating a persistent vegetative state, and 1 indicating death. We grouped Grades 4 and 5 into a “good outcome” group and 1–3 into a “poor outcome” group.

Statistical Analysis

For statistical analysis, we used a commercially available software package (SPSS 20.0, SPSS Inc.). Age, ADC value, and GOS scores were compared by 1-way ANOVA, while GCS scores and sex were analyzed with the chi-square test. We also compared TBI patients exhibiting different secretory dysfunctions (gonadotropin deficiency, thyrotropin deficiency, corticotropin deficiency, GH deficiency, hyperprolactinemia) using unpaired t-tests with the absolute ADC values as independent variables. In addition, we tested the correlation between hypopituitarism and ADC value using the Spearman correlation test and ROC curve. We also investigated the correlation between the ADC value and neurological outcome.

Results

Demographic and clinical data, including age, sex, time of MRI scan from injury, and initial GCS, were available for all 164 TBI patients included in this study (Table 1). The age of the TBI patients (mean 47.7 ± 3.6 years) was similar to that of the controls (mean 49.2 ± 5.3 years, p = 0.86), as was the proportion of men (57.3% [94 of 164] vs 56.7% [17 of 30], p = 0.91). Analysis of the incidence of hypopituitarism by initial GCS score revealed an incidence of 63.5% (40 of 63 patients) in the group with an initial GCS score of 3–8, 58.3% (28 of 48 patients) in the group with a score of 9–12, and 30.2% (16 of 53 patients) in the group with a score of 13–15 (p < 0.01, Fig. 2).

Hormone Profiles

The total incidence of hypopituitarism was approximately 51.2% at 6 months after TBI. Each hormone profile is listed in Fig. 3. The most frequent deficiency (54 cases

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TABLE 1. Summary of demographic and clinical characteristics of TBI patients and controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TBI</th>
<th>HPT</th>
<th>No HPT</th>
<th>Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in yrs</td>
<td>47.7 ± 3.6</td>
<td>45.3 ± 4.1</td>
<td>53.7 ± 7.2</td>
<td>49.2 ± 5.3</td>
<td>0.86*</td>
</tr>
<tr>
<td>Sex: male/female</td>
<td>94/70</td>
<td>50/34</td>
<td>44/36</td>
<td>17/13</td>
<td>0.91*</td>
</tr>
<tr>
<td>GCS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–8</td>
<td>40</td>
<td>23</td>
<td></td>
<td></td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>9–12</td>
<td>28</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13–15</td>
<td>16</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC</td>
<td>1.83 ± 0.16</td>
<td>4.13 ± 0.33</td>
<td></td>
<td></td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.32 ± 0.09</td>
<td>2.28 ± 0.17</td>
<td></td>
<td>0.02†</td>
</tr>
<tr>
<td>GOS score</td>
<td>3.6 ± 0.2</td>
<td>3.4 ± 0.3</td>
<td>4.3 ± 0.2</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

HPT = hypopituitarism; NA = not applicable.
* For comparison between the TBI group and control group.
† For comparison between the HPT subgroup and no-HPT subgroup.
[32.9%]) was gonadotropin deficiency. Growth hormone deficiency was also relatively common (47 cases [28.6%]), as was thyroid hormone deficiency (46 cases [28%]), followed by abnormal prolactin levels (41 cases [25%]). Corticotropin deficiency was quite infrequent (23 cases [14.0%]).

Mean Pituitary ADC in Control and Patient Groups

TBI patients, overall, showed a significant decrease in pituitary ADC compared with controls (1.83 ± 0.16 vs 4.13 ± 0.33, p < 0.01; Fig. 4). In TBI patients with hypopituitarism, the pituitary ADC was further decreased compared with that in TBI patients with normal pituitary function (1.32 ± 0.09 vs 2.28 ± 0.17, p < 0.05; Fig. 4). Furthermore, there was a correlation between the pituitary ADC and the presence of hypopituitarism in TBI patients (r = 0.710, p < 0.01). According to the ROC curve, the pituitary ADC predicted the occurrence of hypopituitarism. The area under the curve was 0.891, with a sensitivity of 90.0% and a specificity of 90.9% at the ADC value of 1.720 (Fig. 5).

Subgroup Analyses Based on Hormone Types

We further evaluated the relationship between the ADC value and different types of hypopituitarism. A significant difference in pituitary ADC was only found between TBI patients with higher prolactin levels and those with normal prolactin levels (p = 0.043). However, the ADC values did not differ significantly between patients with other types of hypopituitarism (Table 2).

Neurological Outcome

At 6 months’ follow-up, neurological outcome was assessed in all patients with TBI by means of the GOS. The mean pituitary ADC in the poor outcome group (GOS score 1–3) was markedly lower than that in the good outcome group (GOS score 4 or 5) (1.52 ± 0.16 vs 2.35 ± 0.23, respectively; p < 0.01; Fig. 6). Furthermore, the pituitary ADC value was positively correlated with the GOS score at 6 months after injury (r = 0.602, p < 0.05), even af-

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Table 2. Mean ADC values for patients with and without different hormonal level abnormalities

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>With Abnormality</th>
<th>Without Abnormality</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonadotropin deficiency</td>
<td>1.49 ± 0.18</td>
<td>1.87 ± 0.22</td>
<td>0.32</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>1.74 ± 0.22</td>
<td>1.91 ± 0.31</td>
<td>0.79</td>
</tr>
<tr>
<td>Thyrotropin deficiency</td>
<td>1.57 ± 0.21</td>
<td>1.71 ± 0.29</td>
<td>0.24</td>
</tr>
<tr>
<td>Higher PRL level</td>
<td>1.31 ± 0.12</td>
<td>2.00 ± 0.11</td>
<td>0.04</td>
</tr>
<tr>
<td>Corticotropin deficiency</td>
<td>1.70 ± 0.36</td>
<td>1.54 ± 0.23</td>
<td>0.91</td>
</tr>
</tbody>
</table>

PRL = prolactin.
Discussion

In this study, we found that the mean ADC in the pituitary was reduced in our cohort of 164 TBI patients, which correlated with neurological outcome at 6 months postinjury. Patients with hypopituitarism following TBI had lower ADC values and worse neurological outcome than TBI patients with normal pituitary function. We conclude that ADC, which reflects mean tissue water diffusivity, appears to be a measure of functional damage in the pituitary following TBI.

The ADC provides an initial measure of movement of water molecules limited by interactions of the diffusing molecules within cellular structures. Changes in the size, shape, and composition of any physical barriers to diffusion will affect the diffusivity of tissue water. In human studies from the early phase after TBI, decreased ADC values have been observed in white matter lesions visible on DWI, and such changes are considered to reflect microstructural pathology. Focal areas of decreased ADC have also been reported in rodent and human studies at 3–18 months after TBI; these changes have been reported in the pons, caudate nucleus, temporal and parietal lobes, and corpus callosum. The areas of decreased ADC were associated with microstructural damage and gliosis on histopathological examination, suggesting evidence of chronic pathological changes.

Few clinical studies using DWI following TBI have addressed the detection of hypopituitarism, which is often diagnosed by serology. However, in some settings, serological confirmation of hypopituitarism following TBI may not be performed until 6–12 months postinjury, and postponing diagnosis until this chronic stage markedly delays initiation of treatment. Therefore, an early and noninvasive diagnostic tool may be useful in the clinical setting. A decreased ADC following acute brain insult was previously reported to be associated with cerebral ischemia. Furthermore, pituitary infarction is one of the most common pathological phenotypes in TBI patients with pituitary deficiencies, which suggests anatomical evidence for hypopituitarism following TBI.

In examining ADC values in TBI patients stratified by secretory function with respect to different types of pituitary hormones, we found that the only comparison that showed a significant difference in pituitary ADC values was between patients with abnormal prolactin levels and those with normal prolactin levels. The patients with abnormal prolactin levels manifested lower pituitary ADC values than those with normal prolactin levels; there were no differences in ADC in other types of hypopituitarism. However, this finding did not support a role for pituitary ADC values in differentiating different status of hormone secretion because of the small sample size and statistical power. Thus, we analyzed the correlation of ADC with GOS score, an important outcome evaluation system for TBI patients. To the best of our knowledge, the relationship between the pituitary ADC and the GOS score in TBI patients has not been previously reported. We found a positive correlation between pituitary ADC values and GOS scores in TBI patients, even after controlling for initial GCS score. These data suggest that hypopituitarism may contribute to the neurological outcome of TBI patients, consistent with previous reports. A relationship between TBI severity and the risk of pituitary dysfunction has also been reported. Thus, the relationship between outcome and pituitary ADC value in our study may be a reflection of injury severity. Studies on larger patient populations are underway to evaluate the relationship between radiological markers in the pituitary and other assessment systems, including quality of life, and cognitive and psychiatric comorbidities in patients with TBI.

There are several limitations of our study. First, the ROI was only focused on the pituitary area, and we did not differentiate the anterior part from the whole pituitary. Furthermore, we did not include the hypothalamus. Kibayashi et al. reported that hypothalamic lesions were always accompanied by pituitary lesions, while lesions in the hypothalamus can result in diabetes insipidus in the same way as lesions in the posterior lobe of the pituitary gland. However, we did not investigate the prevalence of central diabetes insipidus, as it is not associated with the hormones we assessed. We also excluded patients with hormone treatments that would affect the secretion status of pituitary hormones. Therefore, we could not address the effect of hormone replacement on pituitary function at a chronic stage of TBI. Another limitation is that we used an unspecific test for GH. Other studies have reported that GH deficiency was the most common type of hormonal abnormality in TBI patients with hypopituitarism. However, in our study, we found the incidence of GH deficiency was a slightly less than that of gonadotropin deficiency. This discrepancy might be due to the test method itself. We were also unable to measure hormone levels in the control group, as the definition of hypopituitarism was based on the comparison with the normal range according to the laboratory method. Finally, there may have been some differences between subjects with respect to the manual placement of the ROIs, and we cannot exclude partial volume effects since some of the ROIs were placed near the sella turcica. Future studies are required to clarify the different roles of pituitary ADC in the anterior and posterior parts and also adopt more consistent radiological and laboratory methods.

Conclusions

We demonstrated a decrease in pituitary ADC in a subset of TBI patients, which correlates with prolactin secretion status and neurological outcome. Thus, ADC may be a novel radiological marker to predict the occurrence of hypopituitarism in TBI patients and their neurological outcome.

References


Author Contributions
Conception and design: Ping. Analysis and interpretation of data: Zheng, He, Zeng. Drafting the article: Zeng. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Zheng. Statistical analysis: Tong. Administrative/technical/material support: Tong. Study supervision: Tong.

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