Correlation between Cognitive Deficits and Tensor Magnetic Resonance Parameters in Patients with Chronic Diffuse Axonal Injury

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ABSTRACT

Background: The apparent diffusion coefficient (ADC) values and the fractional anisotropy (FA) values calculated from diffusion tensor imaging (DTI) in the acute stage of diffuse axonal injury (DAI) are mainly used for prediction of prognosis. However, neuropsychological outcome correlates more closely with magnetic resonance imaging (MRI) findings from the chronic stage than with those obtained during the acute phase. The purpose of the study was to design a protocol that will assess the spread of neural deficit and provide an accurate prognosis for patients with DAI.

Methods: We compared ADC values and FA values calculated from DTI of the anterior and posterior corpus callosum in four patients (mean ± SD: 24.0 ± 4.5 years) with DAI and cognitive disorders with those of 10 normal control subjects (23.3 ± 1.3 years). All patients had chronic-stage DAI with no significant MRI abnormality. Although they maintained self-care task, they were unable to adapt to social life because of cognitive disorders.

Results: For the anterior corpus callosum, the FA values were higher and the ADC values were lower bilaterally in DAI patients than in the control subjects. The high FA values may be designated as pseudo-FA values due to the gliosis of astrocytes around the degenerated nerve fibers in the anterior corpus callosum.

Conclusions: Our results suggest a close association between pseudo-FA values and low ADC values of the anterior corpus callosum and cognitive disorders in patients with DAI who show no significant MRI abnormalities.

INTRODUCTION

In Japan, there are approximately 280,000 new cases of traumatic brain injury (TBI) each year.[1] In the United States, that number is about 2 million a year,[2] making TBI a major public health problem in both countries. While most cases are classified as mild, about 30% of TBI patients develop some cognitive disorders.[3] Patients who have TBI-related diffuse axonal injury (DAI) are the ones most likely to develop marked cognitive, emotional, and memory deficits, and have serious social problems.[4] Furthermore, many of these patients are young males of about 20 years of age who face problems related to school enrolment or finding work and thus require intensive rehabilitation to continue their education and/or employment.

Based on neuropathological examination and experimental neurotrauma studies, DAI is classified into three grades.[5] In grade 1, there is histological evidence of axonal injury in the white matter of the cerebral hemispheres, corpus callosum, brainstem, and, less commonly, the cerebellum. In grade 2, there is also a focal lesion in the corpus callosum; and in grade 3 there is also a focal lesion in the dorsolateral quadrant or quadrants of the rostral brainstem. Other studies indicated that axonal damage could be present even in patients who do not show clinical evidence of DAI.[6]

In general clinical terms, it is convenient to view head injuries as consisting of three distinct varieties: skull injuries, focal injuries, and diffuse brain injuries.[7] Diffuse brain injury is classified into mild concussion, classic cerebral concussion, and DAI. DAI is further classified, using Gennarelli's classification, into three categories (mild, moderate, and severe) based on the duration of traumatic coma not due to mass lesion.[8]

We often rely on brain imaging for the diagnosis and assessment of the severity of brain damage. However, it is often difficult to predict the prognosis of patients with DAI even with the use of computed tomography (CT) or magnetic resonance imaging (MRI), including T2-weighed images.[9,10] Neuropsychological outcome correlates more closely with MRI in the chronic stage than with MRI in the early stage. In this regard, late ventricular enlargement is particularly associated with poor outcome. Wilson et al[11] concluded that functionally significant abnormalities might only be fully apparent on late scanning. Kamikubo et al[12] found 32 DAI cases among 234 TBI cases assessed by Gennarelli's classification. They reported that although all 32 DAI cases had cognitive disorders, two had no significant MRI abnormalities in the chronic stage. The presence of enlarged lateral ventricles, indicative of cerebral atrophy, in the chronic stage often makes it easy to diagnose DAI. Kamikubo's results, however, point to the limitation of conventional imaging studies and the fact that failure of such techniques to detect abnormalities could jeopardize rehabilitation therapy in TBI patients with cognitive disorders.

Several studies have recently reported the effectiveness of diffusion-weighted imaging (DWI) for evaluation of DAI.[13-16] Diffusion tensor imaging (DTI), a relatively novel MRI technique, is designed to detect more extensive abnormalities than conventional MRI in patients with severe head injury, and the findings of DTI have been reported to correspond with clinically determined neurological deficit.[14] The apparent diffusion coefficient (ADC) values and the

Table 1. Profiles of the four patients with diffuse axonal injury.

Patient	Sex	Preinjury vocational state	Education		Age at time of injury (years)	Cause of brain injury
			Years	Level		
1	M	Athlete	12	HSG	28	TA
2	M	Part-time employee	12	HSG	19	TA
3	M	Office worker	12	HSG	24	TA
4	F	College student	13	HSG	19	TA

HSG=high school graduate
TA=traffic accident

fractional anisotropy (FA) values calculated from DTI in the acute stage of DAI are mainly used for prediction of prognosis.[15,16] To our knowledge, there are no reports that have evaluated the association between ADC values and FA values or problem of cognitive disorder in patients with chronic DAI.

The main purpose of this study was to design a protocol that will assess the spread of neural deficit and provide an accurate prognosis for patients with DAI. Specifically, we compared the ADC and FA values in regions of interest (ROI) between DAI patients with cognitive disorders and a normal control group. All patients had chronic-stage DAI with no significant MRI abnormality. Although they were able to maintain self-care task (dressing, eating, bathing, grooming, use of the toilet, and mobility within the home), they were unable to adapt to social life because of cognitive disorders.

MATERIALS AND METHODS

The control group consisted of 10 healthy male college students aged 20 to 24 years (mean ± SD: 23.3 ± 1.3 years). Four patients with DAI participated in the study. The period between onset and enrolment was more than 6 months in these patients and all were able to complete some neuropsychological tests. The clinical profile of these patients is shown in Table 1. Their age ranged from 20 to 30 years (mean: 24.0 ± 4.5 years). The diagnosis of DAI was based on Gennarelli's classification, with consciousness disturbance maintained for ≥6 hours.[8] The research protocol was approved by the Ethics review Committee of the participating institutions and a signed consent from was obtained from each subject. Neuropsychological tests, consisting of Wechsler adult intelligence scale-revised (WAIS-R), Trail making test (TMT), Paced auditory serial addition task (PASAT), and Miyake paired verbal association learning test (Miyake Memory test), were performed in DAI patients. We used WAIS-R to check for intelligence impairment, PASAT and TMT to check for attention disorders (selective and divided attention), and Miyake Memory test for memory disorders.

MR Image Acquisition

MR images were acquired in all patients and control subjects with the use of a clinical 1.5-Tesla MR imaging unit (23 mT/m maximum amplitude, 77 mT/m/msec slew rate). Diffusion tensor imaging was performed with a modified 2-dimensional dual spin echo type echo planar imaging acquisition window and two pair of diffusion gradients symmetrically positioned around each 180º-

Severity of injury	Time from injury to inspection (years)	At inspection		
		Motor disturbance	Age (years)	Vocational status
Moderate	2	None	30	Vocational aid center entrance
Severe	1.5	None	21	Rehabilitation home entrance
Severe	1.5	None	25	Rehabilitation home entrance
Severe	0.5	None	20	College student

radiofrequency pulse with ramped sampling read-out gradients. The imaging parameters were 10000/111.7/1 [TR/TE/NEX], 24-cm field of view (FOV), 256 x 256 acquisition matrix, 6-mm section thickness, 1242 sec/mm^2 b values for total acquisition.

Data Analysis

The overall translational water motion, characterized by the ADC values, and the anisotropic component of water diffusion, characterized by the FA values, were calculated on a voxel-by-voxel basis. MRI image data were transformed to a standard MRI template into the Talairach Atlas, using SPM2b (Welcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (Mathworks Inc, Natick, MA). We used the MR diffusion tensor analysis software, TENSOR Visualizer (dTVII), developed by the Department of Radiology, Image Computing & Analysis Laboratory, The University of Tokyo Hospital. The 30-voxel ROI was set on the anterior and posterior corpus callosum of the right and left. The ADC and FA values were measured for each part in order to compare the TBI group with the healthy subject group. All data were expressed as mean ± standard deviation (SD). Differences between groups were examined for statistical significance using the Mann-Whitney U-test. A P value < 0.01 denoted the presence of a statistically significant difference.

RESULTS

Table 2 shows the ADC and FA values for each ROI in the control subjects and patients. In the anterior corpus callosum on both sides the ADC values were significantly lower and the FA values were significantly higher in the DAI patients than in the control group. In the right and left posterior corpus callosum the ADC values were significantly lower in the DAI patients compared with the control, and the FA value were not significantly different between the two groups.

Patient 1 had no motor impairment. In this case, the results of neuropsychological tests (Table 3) were within the normal range on the WAIS-R, and were low score on the TMT and PASAT, compared with the control. Thus, although intelligence was comparatively maintained, disorders of attention (selective and divided attention) were recognized in this patient. He was judged to have difficulty being able to ride a bicycle as cycle racer again due to neurofatigue and adynamia. He has retired and currently receives pension for the disability. Moreover, he described being short temper while driving, because of disinhibition, though neurophysiological test did

Table 2. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values of the anterior and posterior corpus callosum in patients with diffuse axonal injury and healthy control.

	Control (n=10)	Patients (n=4)
Anterior corpus callosum		
Right FA value	0.64 ± 0.04	0.75 ± 0.05*
Right ADC value ($x10^{-5}$ cm^2/s)	1.10 ± 0.08	0.76 ± 0.06*
Left FA value	0.64 ± 0.04	0.76 ± 0.02*
Left ADC value ($x10^{-5}$ cm^2/s)	1.08 ± 0.09	0.73 ± 0.02*
Posterior corpus callosum		
Right FA value	0.64 ± 0.02	0.66 ± 0.07
Right ADC value ($x10^{-5}$ cm^2/s)	1.10 ± 0.05	0.96 ± 0.06*
Left FA value	0.64 ± 0.03	0.67 ± 0.04
Left ADC value ($x10^{-5}$ cm^2/s)	1.13 ± 0.08	0.96 ± 0.05*

All data are presented as mean ± standard deviation.
*P<0.01 by Mann-Whitney's U test

not identify this change, a factor that negatively influenced his return to work. With regard to Patient 2, no motor impairment was noted and neuropsychological tests (Table 3) showed low scores for WAIS-R and TMT compared with normal values. The score of PASAT was within the normal range. Non-paired test showed a significant decrease of Miyake paired test. Neurophysiological tests showed no major abnormalities, although disinhibition was evident in social life together with persistent memory disorder. The patient was admitted to a rehabilitation center for further management and the likelihood of starting work again is slim at present.

Patient 3 showed no motor impairment. Performance intelligence (PIQ) in WAIS-R showed a clear decrease and constructive disability was doubted. The scores of TMT, PASAT, and Miyake paired test were low compared with the normal values. Thus, disorders of attention (selective and divided attention) and memory disorder were recognized. Socially, he showed disinhibition. The patient was admitted to a rehabilitation center for further management and was successful in working again in care support service.

Patient 4 showed no motor impairment. Neuropsychological tests (Table 3) showed a normal WAIS-R score. The scores of TMT, PASAT, and Miyake paired test were lower than normal. Though intelligence was maintained, disorders of attention (selective and divided attention) and memory disorder were recognized. In social life, she had severe memory disorder, persistence, and disinhibition. The patient had returned to college and managed well with the help of other students. However, she found it difficult to follow the classes because of severe memory disorder. Furthermore, several of her friends have left her because of the disinhibition. While work related to the field of education will be difficult assuming completion of the course and graduation, it is anticipated that the patient might find work in the welfare field.

DISCUSSION

Several studies of patients with acute DAI reported low FA and ADC values in the corpus callosum compared with the control.[15, 16] Interestingly in our study, the FA values of the anterior cor-

Table 3. Results of neuropsychological tests of patients with diffuse axonal injury.

	WAIS-R			TMT			Miyake Paired Test	
	VIQ	PIQ	FIQ	A	B	PASAT	Paired	Non-paired
Normal range		100 ± 15 (mean ± SD)		66.9	83.9	46.3-41.2	6.6-9.9, 10-10, 10-10	3,2-7.0, 6.6-10 7.7-10
Patient 1	91	91	90	144*	165*	40*	10, 10, 10	4, 8, 7*
Patient 2	70*	87	73*	83*	95*	59	10, 10, 10	3, 4*, 5*
Patient 3	86	60*	72*	124*	206*	29*	7, 9*, 10	1*, 3*, 4*
Patient 4	107	107	106	80*	88*	41*	7, 8*, 8*	2*, 3*, 3*

*Findings outside normal range
WAIS-R=Wechsler adult intelligence scale-revised
TMT=Trail making test
PASAT=paced auditory serial addition task
Miyake Paired Test=Miyake paired verbal association learning test

pus callosum were significantly higher, while the ADC values were lower in DTI patients than in the control group. On the other hand, the FA values of the posterior corpus callosum were not significantly different and the ADC values were lower in DTI patients compared controls. The high FA values and low ADC values of the anterior corpus callosum may reflect frontal lobe abnormality based on the results of neuropsychological tests. Such a rise in the FA values may be designated as pseudo-FA values due to gliosis of astrocytes around degenerated nerve fibers in the anterior corpus callosum. In each patient with DAI, the nerve fibers radiating from the corpus callosum to the frontal lobe showed some damage and it was considered that such damage affected the uniform direction of the axons in the corpus callosum.

In the future, analysis of a larger number of patients, especially DAI patients, is necessary, including histopathological examination. On the other hand, based on the lack of change in the FA values and the low ADC values, accompanied by low diffusion in the posterior corpus callosum, it is conceivable that this area is spared any nerve degeneration. Considered together, our results suggest that our patients with DAI are vulnerable to nerve degeneration in the anterior more than posterior corpus callosum.

It is difficult to detect cognitive disorders in DAI patients using conventional parameters of MRI and single photon emission computed tomography (SPECT). Diffusion white matter injury is not readily visualized by conventional MRI apart from indirect findings such as late ventricular dilatation caused by periventricular white matter degeneration and changes in the corpus callosum.[17] Our results indicate that cognitive disorders can be easily evaluated by objective measurement of the ADC and FA values using DTI, and that this technique is useful for the clinical evaluation of cognitive disorders in patients with chronic DAI who have no significant MRI abnormality.

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REFERENCES

1. Ono J. Epidemiology of traumatic brain injury in Japan. *Jpn J Acute Med*. 2001;25:1527-1531.
2. Kraus J, Nourjah P. The epidemiology of mild head injury. In: Levin H, Eisenberg H, Benton A, eds. *Mild Head Injury.* Oxford: Oxford University Press; 1989:8-22.
3. Mittl RL, Grossman RI, Hiehle JF, et al. Prevalence of MR evidence of diffuse axonal injury in patients with mild head injury and normal head CT findings. *AJNR Am J Neuroradiol.* 1994;15:1583-1589.
4. Levin HS, Mattis S, Ruff RM, et al. Neurobehavioral outcome following minor head injury: A three-center study. *J Neurosurg*. 1987;66:234-243.
5. Adams JH, Doyle D, Ford I, et al. Diffuse axonal injury in head injury: definition, diagnosis and grading. *Histopathology*. 1989;15:49-59.
6. Graham DI, Gennarelli TA, McIntosh TK. Trauma. In: Graham DI, Lantos PL, eds. *Greenfiels's Neuropathology*. Seventh edition. Oxford: Oxford University Press; 2002:823-898.
7. Langfitt TW, Gennarelli TA. Can the out come from head injury be improved? *J Neurosurg.* 1982;56:19-25.
8. Gennarelli TA. Emergency department management of head injuries. *Emerg Med Clin N Am*. 1984;2:749-760.
9. Gentry LR, Godersky JC, Thompson B, et al. Prospective comparative study of intermediate-field MR and CT in the evaluation of closed head trauma. *AJR Am J Roentgeno.l* 1988;150:673-682.
10. Kelly AB, Zimmerman RD, Snow RB, et al. Head trauma: comparison of MR and CT—experience in 100 patients. *AJNR Am J Neuroradiol.* 1988;9:699-708.
11. Wilson JT, Wiedmann KD, Hadley DM, et al. Early and late magnetic resonance imaging and neuropsychological outcome after head injury. *J Neurol Neurosurg Psychiatry.* 1988;51:391-396.
12. Kamikubo T, Ohashi M, Hashimoto K, et al. Cognitive dysfunction in 32 diffuse axonal injury cases. *No To Shinkei.* 2003;55:669-673 (Japanese).
13. Liu AY, Maldjian JA, Bagley LJ, et al. Traumatic brain injury: diffusion-weighted MR imaging findings. *AJNR Am J Neuroradiol.* 1999;20:1636-1641.
14. Wieshmann UC, Symms MR, Clark CA, et al. Blunt-head trauma associated with widespread water-diffusion changes. *Lancet.* 1999;353:1242-1243.
15. Arfanakis K, Haughton VM, Carew JD, et al. Diffusion tensor MR imaging in diffuse axonal injury. *AJNR Am J Neuroradiol*. 2002;23:794-802.
16. TA, Schwamm LH, Schaefer PW, et al. Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. *AJNR Am J Neuroradiol.* 2004;25:370-376.
17. Levin HS. Neuroplasticity following non-penetrating traumatic brain injury. *Brain Inj*. 2003;17:665-674.