Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Coma Duration Prediction in Diffuse Axonal Injury: Analyses of Apparent Diffusion Coefficient and Clinical Prognostic Factors

W.B.Zheng[1*], G.R.Liu[1] , K.M. Kong[2*] and R.H.Wu [1]

Abstract—**Purpose: To evaluate the hypothesis that the Apparent Diffusion Coefficient (ADC) values combined with initial clinical factors indicates the depth of shearing lesions in the brain structure and therefore relates to coma duration of diffuse axonal injury (DAI). Material and Methods: Seventy－four adult patients (48 male and 26 female patients) with diffuse axonal injury were examined with convention MR imaging and diffusion weighted MR imaging between 2 hours and 20 days after injury. Apparent diffusion coefficient (ADC) maps were obtained and the mean ADC values of each Region of Interest （ROI ） were measured using MRI console software. The lesions involvement of brainstem, deep gray matter, and corpus callosum were determined for each sequence separately as well as for the combination of all sequences. The correlations between magnetic resonance (MR) imaging findings of presence of apparent brain injury combined with initial clinical factors were investigated. Results: Clinical characteristics, such as initial score on the Glasgow Coma Scale (GCS), age, and the number of all lesions, ADC scores of the patient in MR findings were predictive of the duration of coma. Conclusion: Post-traumatic coma duration of DAI could be predicted by cerebral MRI findings in the acute to subacute stage after head injury combined with clinical prognostic factors. Age, ADC scores, GCS, number of lesions are highly significant in predicting coma duration. The technique presented herein might provide a tool for in vivo detection of DAI for the coma duration at the early stages in patients with traumatic brain injury.**

Keyword—**Diffuse axonal injury; Magnetic resonance imaging; Diffusion-weighted imaging; Apparent diffusion coefficient**

Ⅰ. INTRODUCTION

DIFFUSE brain injury are commonly produced by motor vehicle crashes, and in some cases, falls and assaults [1,2]. Axonal damage is one of the most common and important pathologic features of traumatic brain injury. In DAI at high severity, the axonal pathology is accompanied by tissue tears in the white matter with intraparenchymal hemorrhage usually located centrally in the corpus callosum corpus, basal ganglia, and dorsolateral region of the rostral brainstem. This level of DAI is associated with prolonged unconsciousness, high mortality, and poor outcome in survivors. Various clinical and laboratory tests have failed to predict recovery so we assessed the value of cerebral magnetic-resonance imaging (MRI) in prediction of recovery. Magnetic resonance imaging (MRI) studies over the past decade have clarified the imaging features of diffuse axonal injury and have proved invaluable in diagnosis. A clear correlation between clinical outcome and the depth of the diffuse axonal lesions in the central brain structures on MRI has been reported [3,4,5]. Recently , new imaging techniques—such as diffusion weighted imaging (DWI)—were reported to be superior to the convention MR image for the early detection of traumatic white matter lesions[6,7,8]. Diffusion weighted imaging (DWI) is a non-invasive technique, that is capable of probing the structure of biologic tissues at a microscopic level and may therefore be used for in vivo tissue characterization [9].The principle of DWI exploits the random, translational motion of water protons in biologic tissues [10]. On diffusion sensitive sequences this motion causes phase dispersion of the spins resulting in signal loss [11,12].This signal loss can be quantified by calculating the apparent diffusion coefficient (ADC), which refers to the specific diffusion capacity of a biologic tissue [13,14].

Diffusion-weighted imaging can demonstrate lesions that are not visualized with conventional MR sequences[15] .In addition, the results of previous animal and human studies show that lesions with decreased or increased diffusion occur in head trauma [16,17,18] , a finding that suggests that diffusion-weighted imaging may enable differentiation of cytotoxic from vasogenic edema in diffuse axonal injury. Decreased ADC values can be observed in traumatic brain injury[17,19] .Thus, the purpose of our study was to determine whether diffusion-weighted imaging findings and decreased ADC could be applied to predict coma duration more effective in diffuse axonal injury.

Ⅱ. METHODOLOGY

Patients

Seventy－four adult patients (48 male and 26 female patients; mean age, 24.2 years; age range, 21–72 years) who were consecutively admitted to the Medical Centre of Acute Medicine of an university hospital between September 2002 and March 2005. All the patients had been admitted directly from the scene of an traffic accident within an hour after sustaining their injuries. Brain MRI was performed within 2 hours to 20 days after admission for those unconscious patients with head injury who did not have evidence of an intracranial mass lesion on computed tomography (CT) which was routinely performed within 2 hours after admission. None of the 74 patients had severe life threatening injuries to other organs. Patients with diffuse axonal injury fulfilled the following criteria: a) Immediate and prolonged posttraumatic unconsciousness from the time of injury no cause of unconsciousness found other than the primary brain injury; b) The presence of white matter injury on MRI, there was not a prior history of clinically important hypertension, diabetes mellitus, cerebrovascular disease, or another chronic medical problem that might lead to imaging abnormalities similar to those described for diffuse axonal injury. The location and appearance of diffuse axonal lesions were assessed by an

* Corresponding authors: W.B.Zheng and K.M. Kong', the 2nd Hospital, Shantou University Medical College, Shantou, China (e-mail: hwenb@21cn.com, kongkm@vip.sina.com)
1. Department of Medical Imaging, the 2nd Hospital, Shantou University Medical College, Shantou, Guangdong, 515041, China
2. Department of Orthopeadics, the 2nd Hospital, Shantou University Medical College, Shantou, Guangdong, 515041, China

attending neuroradiologist who were blinded to the clinical status of the patients.

Volunteer Characteristics

All subjects provided written informed consent before their enrollment in the study. The study included 100 healthy volunteers chosen from a healthy population (50 men and 50 women), whose ages ranged from 21 to 72 years old. A neurologist interviewed and examined the volunteers before imaging and excluded those for whom MR imaging was contraindicated. The volunteers had no symptoms, signs, or history of any neurologic or systemic disease that might have affected the brain (eg, diabetes, chronic obstructive pulmonary disease, hypertension, metabolic disorders), nor did they have a family history of dementia or multiple sclerosis. Subjects in whom MR images revealed an unexpected cerebral lesion were excluded. All subjects were examined with MR imaging, including conventional and diffusion-weighted imaging in three orthogonal directions with two b values (0 and 1000 s/mm^2) at 1.5 T. Bilateral ADCav values were determined in 4 regions of interest encompassing the entire brain. These structures were the gray-white junction, corpus callosum, basal ganglia, and the stem.

Clinical assessment

The Glasgow Coma Score (GCS) has an established place in the management of traumatic brain injury and is the most widely accepted and understood scale. The Glasgow Coma Scale score ranged from 3 (worst score) to 15 (best score) and was based on the combined evaluation of three categories of neurologic function: eye opening, best verbal response, and best motor response. The duration of unconsciousness was defined as the time lapse until simple orders were obeyed with the eyes opening spontaneously. Simple orders suggest the recovery of cognitive acuity to verbal stimuli. Note that unconsciousness may encompass a state of wakefulness (opened eyes) associated with a total lack of cognitive function, which sometimes accompanies a persistent vegetative state [20] .A Glasgow coma scale (GCS) score of 3 to 15 rating was obtained either on admission to the emergency room or at the scene. Two consulting neurosurgeons confirmed the duration of unconsciousness in each patient. Pupil size and reactivity were assessed and recorded at the same time as the GCS.

MR Imaging

Seventy－four adult patients were examined with conventional MR imaging as well as echo-plan diffusion-weighted MR imaging in 2 hours to 20 days after traumatic injury. All scans were obtained on a GE 1.5T MR scanner. The following sequences were applied: (a) transverse T2-weighted fast spin-echo (SE) (repetition time msec/echo time msec, 4000–5000/108; field of view, 240 x 180 mm; matrix, 256 x 192; section thickness, 7 mm; echo train length, eight; signals acquired, two), (b) transverse FLAIR (repetition time msec/echo time msec/inversion time msec, 11000/125, TI = 2200; field of view, 240 x 180 mm; matrix, 256 x 192; section thickness, 5 mm; one signal acquired), (c) transverse T2*-weighted GRE (750/25; flip angle, 20°; field of view, 240 x 180 mm; matrix, 256 x 192; section thickness, 5mm; number of signals acquired, two), and (d) Diffusion-weighted image was performed using a spin-echo echo-planar sequence (9999/112, field of view = 24, matrix = 128×128). For DWI, 2 b values (b=0 and b=1000 s/mm^2) were used. The gradients were applied to each of the *x*-, *y*-, and *z*-directions and the calculated isotropic images were used for further analysis of the DWI intensity maps. The maps of the apparent diffusion coefficient (ADC) were calculated according to the Stejskal–Tanner equation: $ADC=-\ln(SI_{1000}/SI_0)/b_{1000}$, where SI is signal intensity. DWI intensity and ADC values were expressed as the ratio relative to the contralateral homotopic regions.

Lesions were characterized as DAI on the basis of their location and their appearance on conventional MR images. The lesions were hemorrhagic or nonhemorrhagic were evaluated by transverse T2*-weighted GRE images. Regions of interest were drawn on the diffusion-weighted images based on areas of abnormally increased signal intensity, and were applied to the trace maps to obtain the corresponding ADC values. Apparent Diffusion Coefficient Maps were obtained and the mean ADC values of each ROI （Region of Interest） was measured using MRI console software. The total number of lesions was determined for each sequence separately, as well as for the combination of all sequences. The number of lesions with decreased ADC was also determined. In addition, lesions were characterized as DAI by two neuroradiologists on the basis of their location and their characteristics on conventional imaging sequences. The location and appearance of diffuse axonal lesions, especially in the corpus callosum and brain stem, were assessed by two attending neuroradiologist, who were blinded to the clinical status of the patients.

Statistical analysis

All the data were analyzed using SPSS10.0 software. A linear stepwise regression analysis was used to predicting duration of unconsciousness based on clinical variables thought to have probable prognostic values in former studies and MRI findings. To study the average values in the different regions of the brain, percentile of multiple indicatrixes was used for the normal ADC values range of human brain in our study which was considered to be accurate and more convenient than other statistical analysis in early report[21,22].

Ⅲ. RESULTS

Patient characteristics

Most of the patients were men. Among the clinical profiles of the 74 patients, thirty-four patients were injured in motor vehicle accidents, twenty-three patients were pedestrian injured and seventeen patients were bicycle riding injured in a traffic accident. Ages at the time of injury ranged from 21 to 72 years. No severe extra-CNS complications occurred. None of the patients died but three patients were in a vegetative state for six months after the injury. The other 71 patients recovered consciousness within fifteen weeks. Mean (SD) duration of unconsciousness in the patients who recovered was 17.2 days (SD), ranging

from one to 105 days. Time interval between the injury and the scan ranged from 2h to 20days.

MRI findings

Lesion Characterization

The serial combination MRI scans in each patient showed one or more lesions in any one of the four separate areas—the cerebral lobar white matter, the basal ganglia/thalamic, the corpus callosum, and the midbrain. These are common components of the lesions of diffuse axonal injury and are known as the shearing injury triad. An apparent injury on MRI in either of these regions was detected in 74 patients; The total number of lesions depicted with each sequence, as well as the totals for the combination of all four MR imaging sequences, are presented in Table 1. Diffusion-weighted imaging depicted the largest number of lesions, followed by FLAIR, T2-weighted fast SE, and the lowest number of lesions were depicted with T2*-weighted GRE sequences. But the largest number of hemorrhagic lesions were depicted with T2*-weighted GRE sequences. The combination of sequences showed a total of 377 shearing lesions. Of the 317 lesions depicted on diffusion-weighted images showed decreased diffusion on ADC maps. ADCav values of nonhemorrhagic lesions were $0.69\pm0.116\times10^{-3}mm^2/s$ （n＝307） and hemorrhagic lesion were $0.50\pm0.115\times10^{-3}$ mm^2/s（n＝70）. Among the 74 patients, 35 (47%) had lesions in the brainstem, 34 (46%) had lesions within the basal ganglia, and 47 (67%) had injuries of the corpus callosum. Only 15 (21%) had traumatic lesions in all three locations.

Normal reference ADC value

Absolute ADC values may be used to identify the traumatic brain injury tissue precisely, but their use requires a normal reference value for each brain region. Among human DW studies, only a few have involved the use of quantitative measurements [23-25]. Gideon et al [26], in their study of 17 volunteers, found small age-related changes in the white matter but not in the gray matter. Helenius et [27], study 80 healthy adult volunteers of both sexes with a wide age range, found the left and right hemispheres had similar ADC_{av} values, the ADC_{av} values were not affected by aging and no sex difference. In the present study, 100 healthy volunteers with no sexes and age range grouping were examined with spin-echo echo-planar DW imaging to establish reference normal average ADC_{av} values in the various regions of the brain. Percentile of multiple indicatrixes was applied to study the average values in the different regions of the brain and the reference range were as follow ($\times10^3mm^2/s$): gray-white junction≥0.000720, corpus callosum≥0.000815, basal ganglia≥0.000740 and brain stem ≥0.000830.

In general, lesions at the gray-white junction, in the corpus callosum, the basal ganglia/thalamic and at the dorsolateral aspect of the upper brain stem were characterized as DAI. So ADC measurements were obtained from normal-appearing white matter in these regions in all subjects. In each of the 74 patients studied, isotropic diffusion-weighted images showed lesions with increased signal intensity and corresponding decreased ADC. The lowest ADC value of the lesion of each region was selected and was compared with normal ADC values. ADC values scale of the lesion in the 4 ROIs was assigned as four grades. ADC scores of each patient were obtained by summation ADC score of each of the four region which was assigned as 0 to 3 rating.（Table2）

Predictors of duration of unconsciousness

A stepwise regression analysis was done to assess the usefulness of patient characteristics and imaging features in predicting duration of unconsciousness. Regression standardized residual was not normal distribution and near normal distribution when duration of unconsciousness(y) was logarithmic transform. Patient characteristics were included age（χ_1）, Glasgow coma scale score（χ_2）,sex（χ_3 ,1=man, 0=female）, time interval between the injury and the scan（χ_4）, pupil size change or not（χ_5, 1=yes, 0=no）, consciousness state (χ_6, 1=unconsciousness, 2=consciousness recovery). Imaging features were included number of the lesions（χ_7）, ADC scores（χ_8）. The analysis of results is shown in Table 4. The variables such as age（χ_1）, GCS score（χ_2）, total number of cerebral lesions（χ_7）and ADC scores（χ_8） were predictors in the model. Sex（χ_3）, time interval between the injury and the scan（χ_4）, pupil size change or not（χ_5,）, consciousness state (χ_6）were failed to predict duration of unconsciousness ($\hat{y}$) (Table3).

TABLE 1

Total Number of Lesions Depicted with each MR Imaging Sequence

Sequence	Nonhemorrhagic (n=307)	hemorrhagic (n= 70)	total (n=377)
Diffusion weighted *	271	46	317（84%）
FLAIR	176	50	226（60%）
T2-weighted fast SE	136	48	184（49%）
T2*-weighted GRE	100	70	170（45%）

TABLE 2

ADC values scale in the 4 ROIs

Scale	gray-white junction	corpus callosum	basal ganglia	brain stem
3	0.000245～0.000402	0.000433～0.000559	0.000166～0.000353	0.000553～0.000645
2	0.000403～0.000560	0.000560～0.000686	0.000354～0.000537	0.000646～0.000738
1	0.000561～0.000719	0.000687～0.000814	0.000538～0.000739	0.000739～0.000829
0	≥0.000720	≥0.000815	≥0.000740	≥0.000830

TABLE 3

Coma Duration Predictor Variables

Model		B	95%confidence interval for B		*P*
			Lower	Upper	
Constant		0.867	0.637	1.098	
Age	(χ_1)	0.005	0.002	0.008	0.001
GCS=Glasgow Coma Scale	(χ_2)	-0.062	-0.079	-0.046	0.000
Total number of cerebral lesions	(χ_7)	0.041	0.028	0.054	0.000
ADC scores	(χ_8)	0.059	0.028	0.089	0.000

a. Dependent Variable: lg ($\hat{y}$ +1)

Predictors：(constant）, χ_1,χ_2,χ_7,χ_8

$\hat{Y}$ =lg ($\hat{y}$ +1)=0.867+0.0053(χ_1)−0.0624（χ_2）+0.0408（χ_7）+0.0588（χ_8）

F =96.00,P≈0<0.001 R =0.921

$\hat{y}$ =lg^{-1}[0.867+0.0053 (χ_1) -0.0624（χ_2）+0.0408（χ_7）+0.0588（χ_8）]-1

$S_{y,1,\ldots,5}$ =0.1777, $t_{(0.05,74)}$ =1.994

Coma duration Predicted value rang $\lg^{-1}[\hat{Y}- t_{(0.05,74)} S_{y,1,2,3\cdots,m,}] \sim \lg^{-1}[\hat{Y}+ t_{(0.05,74)} S_{y,1,2,3\cdots,m,}]$

□. DISCUSSION

Historically, coma is the most common immediate impairment that has been associated with the severity of DAI. Before the advent of neuroimaging, the characteristics of diffuse axonal injury were defined by Adams et al and Gennarelli et al from a histopathological viewpoint [28,29] .Their experimental studies suggested that centripetal extension of a shearing injury into the brain stem caused prolonged unconsciousness. Furthermore they emphasized the importance of injury to the corpus callosum and dorsolateral midbrain, and described diffuse axonal damage in the cerebral hemispheres.[1] Recent reports by Kampfl and colleagues—who performed detailed analyses of the anatomical location and frequency of lesions—provided evidence that a combination of lesions in the corpus callosum and the dorsolateral upper brain stem was a highly significant MRI feature in post-traumatic vegetative states associated with diffuse axonal injury[30] .

Yanagawa and colleagues reported that the total number of traumatic brain lesions detected by T2* imaging correlated with the duration of unconsciousness [31] .However, the lesions of deep seated diffuse axonal injury are sometimes overlooked or underestimated because the detection of these lesions is unavoidably affected by the performance of the MRI device and by sequencing, time interval between the injury and the scan, and radiological interpretation. Diffusion weighted imaging were reported to be superior to the FLAIR image for the early detection of traumatic white matter lesions. Decreased ADC values can be observed in traumatic brain injury[15,32].

In the study by Barzo et al[33], the reductions in ADC extending out to several weeks, as seen in their experimental animal model, are postulated to result from neurotoxic edema. This slower form of cellular swelling may be responsible for the extended period of time over which decreased ADC values can be observed in traumatic brain injury. An alternative explanation may be related to the presence of microscopic hemorrhage and ruptured axons with membrane fragmentation in DAI, increasing the barriers to the free movement of water molecules, and thereby producing a decrease in ADC. Ebisu et al [34] reported decreased ADC values in hemorrhagic versus nonhemorrhagic infarcts, but could not explain the reason for this finding. In their study, several hemorrhagic lesions (without infarction) were studied, which also displayed persistently decreased ADC. Although the ADCs were decreased in both hemorrhagic and nonhemorrhagic stroke, the values were relatively lower in the hemorrhagic lesions. These were also displayed in our study. The ADC values of the hemorrhagic lesions of DAI is much lower than the nonhemorrhagic lesions. The presence of hemorrhage in DAI-type lesions is a poor prognostic sign[35]. The ADC value might correlate with the depth of the diffuse axonal lesions in the central brain structures clinical severity. We tested the hypothesis that a relatively new MR imaging technique, diffusion weighted imaging and decreased ADC could be applied to predict duration of unconsciousness in diffuse axonal injury. It is necessary to establish quantitative criteria for predicting unconsciousness duration using these techniques combined with the patient factors. Patient factors that determine outcome from traumatic brain injury include severity of primary and secondary injuries, low GCS on presentation[36], advanced age (>60 years)[37]and comorbidities. Ingeneral, a GCS of 14–15 indicatesa mild injury, 9–13 a moderate injury, and 3–8 is classified as severe. In the severely injured, such as intubated patients or those with ocular or facial trauma, the motor response is the most useful. Pupil size and reactivity are important when consciousness is impaired. In the absence of traumatic mydriasis, abnormalities of the pupil size and reactivity may indicate compression of the third cranial nerve, suggesting raised intracranial pressure or impending herniation, particularly when associated with lateralizing motor signs and depressed consciousness. Pupil size and reactivity was failed to predict the duration of unconciousness.

Our study showed that the factors—including Glasgow unconsciousness scale (GCS) score, age, numbers of lesions and ADC scores may play an important role in predicting the outcome of traumatic brain injury. They served as predictors of the duration of unconsciousness, which was the issue of greatest clinical concern in the acute management of such patients. It also provided useful information on prognosis. It showed the correlation between unconsciousness duration and age, number of lesions, the duration of unconsciousness and the age, number of the lesions, ADC scores were direct correlation, and were inverse correlated with Glasgow coma scale score. According the model, we could predict unconsciousness duration more effective in diffuse axonal injury.

The present study demonstrated that post-traumatic duration of unconciouness of DAI could be predicted by cerebral MRI findings in the acute to subacute stage after head injury combined with clinical prognostic factors. Age, GCS, ADC scores and number of lesions are highly significant in predicting unconsciousness duration. The technique presented herein might provide a tool for in vivo detection of DAI for the unconsciousness duration at the very early stages in patients with traumatic brain injury. This could have significant implications not only for the diagnosis but also for the treatment of these patients.

REFERENCES

[1] J.H. Adams, D. Doyle and I. Ford, "Diffuse axonal injury in head injury: definition, diagnosis, and grading,"Histopathol 1989,15: 49–59

[2] P.C. Blumbergs, N.R. Jones and J.B. North "Diffuse axonal injury in head trauma," Neurol Neurosurg Psychiatry,1989, 52: 838–841

[3] H.S. Levin, D. Mendelsohn and M.A. Lilly, "Magnetic resonance imaging in relation to functional outcome of pediatric closed head injury: a test of the Ommaya–Gennarelli model ,"Neurosurgery, 1997, 40: 432–440

[4] M.A. Grados, B.S. Slomine and J.P. Gerring , "Depth of lesion model in children and adolescents with moderate to severe traumatic brain injury: use of SPGR MRI to predict severity and outcome, " Neurol Neurosurg Psychiatr, 2001 70:350–358

[5] L.R. Gentry, J.C. Godersky and B.H. Thompson, "Traumatic brain stem injury: MR imaging," Radiology, 1989,171:177–187

[6] A.Y. Liu, J.A. Maldjian and L.J. Bagley, "Traumatic brain injury: diffusion-weighted MR imaging findings," Am J Neuroradio ,1999,20:1636–1641

[7] D.H. Smith, D.F. Meaney and R.E. Lenkinski, "New magnetic resonance imaging techniques for the evaluation of traumatic brain injury," Neurotrauma, 1995, 12: 603–607

[8] C.C. Hanstock, A. Faden and R.M. Bendall ,"Diffusion weighted imaging differentiates ischemic tissue from traumatized tissue," Stroke,1994, 25: 843-848

[9] D. Le Bihan, "Differentiation of benign versus pathologic compression fractures with diffusion -weighted MR imaging: a closer step toward the'holygrail'of tissue aracterization ,"Radiology,1998, 207: 305-307

[10] A. Szafer, J.Zhongand A.W. Anderson, "Diffusion -weighted imaging in tissues: theoretical models," NMR Biomed,1995, 8:289-296

[11] P. Lang, J.O. Johnston and F. Arenal-Romero "Advances in MR imaging of pediatric musculoskeletal neoplasms," Magn Reson Imaging Clin N Am , 1998, 6:579-604

[12] A. Szafer, J .Zhong, and J.C. Gore "Theoretical model for water diffusion in tissues," Magn Reson Med, 1995, 33: 697-712

[13] M. Eis, T. Els and M .Hoehn-Berlage, " High resolution quantitative relaxation and diffusion MRI of three different experimental brain tumors in rat," Magn Reson Med, 1995,34: 835-844

[14] D. Le Bihan, E. Breton and D. Lallemand,"Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging," Radiology,1998,168: 497-505

[15] T.A. Huisman, A.G. Sorensen and K. Hergan , "Diffusion weighted imaging for the evaluation of diffuse axonal injury in closed head injury," Comput Assist Tomogr ,2003, 27: 5-11

[16] A.W. Unterberg, R. Stroop and U.W. Thomale, "Characterisation of brain edema following 'controlled cortical impact injury' in rats," Acta Neurochir Suppl (Wien) 1997, 70: 106-108

[17] J. Ito, A. Marmarou and P. Barzo "Characterization of edema by diffusion-weighted imaging in experimental traumatic brain injury," Neurosurg, 1996,84: 97-103

[18] P. Barzo, A. Marmarou and P. Fatouros,"Contribution of vasogenic and cellular edema to traumatic brain swelling measured by diffusion-weighted imaging," Neurosurg,1997 87: 900-907

[19] D. Alsop, H. Murai and J. Detre,"Detection of acute pathologic changes following experimental traumatic brain injury using diffusion-weighted magnetic resonance imaging," Neurotrauma, 1996,13:515-521

[20] G. Teasdale and B. Jennet,t" Assessment of coma and impaired consciousness A practical scale," Lancet , 1974,2: 81–84

[21] M.S. Srivastava and E.M. Carter, " An Introduction to Applied Mullivariate statistics,"New York: Elservier Science Publishing Co., Inc: 1983,134-166

[22] B. Chen, K. Li and K. Lin,"Medical reference ranges determined with percentile of multiple indicatrixes," Med J West China,2003 1:185-186

[23] S. Brockstedt, C. Thomsen and R. Wirestam "Quan -titative diffusion coefficient maps using fast spin-echo MRI," Magn Reson Imaging, 1998,16: 877–886

[24] D. Chien, R.B. Buxton and K.K. Kwong " MR diffu -sion imaging of human brain," Comp Assist Tomogr, 1990,14: 514–520

[25] C. Pierpaoli, P. Jezz and P.J. Basser ,"Diffusion tensor MR imaging of the human brain, "Radiology,1996, 201: 637–648

[26] P. Gideon, C. Thomsen and O. Henriksen," Increased self-diffusion of brain water in normal aging," Magn Reson Imaging ,1994,4:185–188

[27] J Helenius, L Soinne and J Perkio,"Diffusion-Weighted MR Imaging in Normal Human Brains in Various Age Groups," AJNR Am J Neuroradiol ,2002,23:194–199

[28] J.H. Adams, D.I. Graham and L.S. Murray, "Diffuse axonal injury due to nonmissile head injury in humans: an analysis of 45 cases," Ann Neurol, 1982, 12:560–563

[29] T.A. Gennarelli, L.E.Thibault and J.H. Adams, "Diffuse axonal injury and traumatic coma in the primate," Ann Neurol ,1982, 12: 564–574

[30] A. Kampfl, G. Franz and F Aichner, "The persistent vegetative state after closed head injury: clinical and magnetic resonance imaging findings in 42 patients.," Neurosurg, 1998, 88: 809–816

[31] Y. Yanagawa, Y. Tsushima and A. Tokumaru, " A quantitative analysis of head injury using T2*-weighted gradient-echo imaging," Trauma ,2000,49: 272–277

[32] D.A. Hammoud and B.A. Wasserman,"Diffuse axonal injuries: pathophysiology and imaging," Neuro imaging, Clin N Am, 2002,12:205-216

[33] P. Barzo, A. Marmarou amd P. Fatouros ,"Magnetic resonance imaging-monitored acute blood-brain barrier changes in experimental traumatic brain injury," Neurosurg,1996, 85:1113-1121

[34] T. Ebisu, C.Tanaka and M. Umeda," Hemorrhagic and nonhemorrhagic stroke: diagnosis with diffusion -weighted and T2-weighted echo-planar MR imaging,"Radiology ,1997,203:823-828

[35] K. Paterakis, A.H. Karantanas and A. Komnoa, "Outcome of patients with diffuse axonal injury: the significance and prognostic value of MRI in the acute phase," Trauma, 2000,49:1071-1075

[36] The Brain Trauma Foundation, The American Association of Neurological Surgeons, "The Joint Section on Neurotrauma and Critical Care Glasgow Coma Scale Score," Neurotrauma, 2000 17:563–572

[37] The Brain Trauma Foundation, The American Association of Neurological Surgeons, "The Joint Section on Neurotrauma nd Critical Care Age," Neurotrauma, 2000, 17:573–582