Int J Clin Exp Med 2019;12(11):13050-13054
www.ijcem.com /ISSN:1940-5901/IJCEM0063601

Original Article

Clinical features, prognosis and treatment of 36 cases of diffuse axonal injury

Qihan Chen, Lin Dan

Department of Neurosurgery, Tonglu First People's Hospital, Xueshen Road, Tonglu, Hangzhou 311500, Zhejiang Province, China

Received June 19, 2015; Accepted December 10, 2018; Epub November 15, 2019; Published November 30, 2019

Abstract: Objective: To analyze the relationships between the clinical features and the prognosis of diffuse axonal injury (DAI) for further comprehensive treatment. Methods: According to the length of time of coma after injury, 36 DAI patients were divided into three groups, namely the mild group, the moderate group, and the severe group. The clinical features, the CT data (Siemens, Germany, 32-slice) and the treatment results of these three groups were analyzed. Results: Among the 24 patients (66.7%) in the severe group, CT scanning within 24 h after injury revealed that 12 patients (50%) had punctiform high-density shadows in different brain regions. Among these 24 patients, 7 patients died, and 9 patients exhibited a good prognosis; among the 7 patients (19.4%) in the moderate group, CT scanning revealed only 2 cases of punctiform high-density shadows inside the brain, and except for 1 case of moderate disability, the rest all exhibited a good recovery. Among the 5 patients (13.9%) in the mild group, CT scanning only found abnormalities in 1 patient (small bleeding in the arachnoid), and all the patients recovered well. When admitted, the moderate-severe group exhibited significantly lower GCS than did the mild group ($P < 0.05$, $P < 0.01$), and the primary coma duration time was significantly longer than it was in the mild group. Conclusions: The patients with traumatic brain injury-caused comas that lasted for more than 6 hours and whose CT scanning could not reveal obvious space-occupying lesions could be diagnosed as DAI. Clinical grading, GCS and primary coma time could help determine the prognosis, and comprehensive treatment might achieve satisfactory effects.

Keywords: Brain injury, tomography, x-ray machine, prognosis, diffuse axonal injury, treatment

Introduction

Diffuse axonal injury (DAI) has a high incidence, its early diagnosis is often unspecific, and conventional CT scanning often gives negative results. However, axonal injury is normally serious, and can cause persistent coma, even death, and its rates of disability and mortality are high and its prognosis poor. Currently, clear diagnostic tools and effective treatment are still lacking. In DAI, axonal structures are often damaged because of acceleration injury-induced shear forces [1]. Meanwhile, small blood vessels in corresponding regions can be ruptured and bleed, and the wider the range, the worse the prognosis [2, 3]. Currently, as for DAI treatment, determining the prognosis is still difficult, and normally, patients with low GCS and bleeding sites at the midline generally exhibit severe clinical symptoms and poor prognoses [4-8]. According to the clinical features of DAI, we summarized a set of CT radiological characteristics, and our department treated 36 DAI patients from April 2010 to September 2012, and their clinical features, diagnoses, and prognoses are summarized below.

Clinical data

General information

This study included 27 males and 9 females. The youngest was 3 years old, and the oldest was 76 years old, the mean age was 38.4 years old. 32 cases were the result of traffic accidents, and 4 cases were the result of falls.

Clinical grouping

DAI diagnostic criteria: brain injury-caused primary coma lasting more than 6 h, cranial CT examination found no obvious space-occupying lesions (intracranial hematoma > 20 ml), and

Table 1. Comparison of basic clinical conditions among the groups ($\bar{x} \pm s$)

group	cases	age (years)	(points)	coma duration (d)
Mild group	5	21.79 ± 4.64	10.02 ± 1.65	0.71 ± 0.19
Moderate group	7	30.54 ± 9.67	7.01 ± 1.08*	4.25 ± 1.72*
Severe group	24	31.25 ± 18.96	5.64 ± 1.22**,Δ	38.87 ± 34.11*

Compared with the mild group: *P < 0.05 **P < 0.01; compared with the moderate group: ΔP < 0.05.

Table 2. Comparison of basic clinical conditions among the patients with different prognoses ($\bar{x} \pm s$)

Prognosis group	cases	age (years)	GCS (points)	coma duration (d)
Death	7	32.56 ± 27.56	4.52 ± 0.75**	37.33 ± 41.8*
(prolonged) agrypnocoma	4	32.01 ± 14.74	4.90 ± 0.75**	91.02 ± 0.00**
Disability	6	27.24 ± 8.76	6.01 ± 0.73*	20.54 ± 16.97
good prognosis	19	28.34 ± 13.45	7.93 ± 1.49	8.76 ± 7.42

Compared with the good prognosis group: *P < 0.05 **P < 0.01.

the midline was basically maintained in the center. According to the post-injury coma period, the patients were divided into the mild group, the moderate group, and the severe group. Mild group: 5 cases, accounting for 13.9%, with post-injury primary coma lasting 6-24 h; moderate group: 7 cases, accounting for 19.4% with post-injury primary coma lasting 24 h-7 days; severe group: 24 cases, accounting for 66.7%, with post-injury primary coma lasting more than 7 days, or if not more than 7 days, signs such as post-injury decerebrate rigidity or brainstem rigidity appeared, and the patient might die in a short time.

CT data of each group within 24 h after DAI

All patients underwent CT scanning within 24 h after injury, and found no significant midline shift, or intracranial hematoma > 20 ml and contusion lesions that were big enough to cause significant space-occupying effects. 6 patients exhibited diffuse brain edema (DBE) in CT within 4 h after injury, and the ventricular system shrank. 18 patients exhibited traumatic subarachnoid hemorrhage (t-SAH).

Treatment methods

No patient underwent surgery. Once clinically diagnosed as DAI, patients with GCS ≤ 8 points were sent to the ICU for treatment. 6 DBE cases underwent tracheotomy and hyperventilation within 3 days after being admitted, and calcium blockers were applied in the early stages. Patients with t-SAH received calcium antagonists, and patients with more subarachnoid hemorrhage underwent lumbar punctures to release blood cerebrospinal fluid, and the rest of the treatments were performed mainly to maintain the metabolic balance of water, electrolyte, blood gas, and blood sugar; their airways were kept open, preventing lung infections and other complications; given adequate nutritional support, neurotrophic drugs, analepsia, and hypothermia treatment, etc. Patients with midline injuries were given hormones, and patients with cranial hypertension were given mannitol.

Statistical methods

All data are expressed as $\bar{x} \pm s$, and the intergroup comparison used the *t* test, with $P < 0.05$ considered as significantly different.

Results

Comparison of basic clinical conditions among the groups

As shown in **Table 1**, there was no significant difference in age among the three groups ($P > 0.05$), but the GCSs of the severe group and the moderate group were significantly lower than the mild group ($P < 0.01$, $P < 0.05$), and their coma durations were also significantly longer than the mild group ($P < 0.05$).

Comparison of basic clinical conditions among the patients with different prognoses

As shown in **Table 2**, the patients with different prognoses were divided into 4 groups, namely death, prolonged coma, disability and good prognosis, and the relationships between basic their clinical conditions when they were admit-

ted and their prognoses were analyzed, and it was found that there was little relationship between age and prognosis, but the relationship between post-injury coma duration and prognosis was close. At the same time, the GCSs, when admitted, of the patients whose prognoses were death or prolonged coma were significantly lower than those with good prognoses ($P < 0.01$), and the patients with good prognoses also exhibited significant differences than those with disabilities ($P < 0.05$).

Analysis of other clinical conditions

① CT Scanning: the mild group had 1 case that exhibited t-SAH (small) in the CT scanning within 24 h after injury; the moderate group had 2 cases of abnormalities, including a skull fracture and t-SAH; and the severe group exhibited abnormal CT scanning results in all cases, including punctiform high density shadow, t-SAH, skull fracture, and brain edema. ② Prognoses: all patients in the mild group exhibited good prognoses; the moderate group had 5 cases of good prognoses, and 2 cases of disabilities; the severe group had 11 cases of adverse prognosis (death and prolonged coma), 4 cases of disabilities, and 9 cases of good prognosis.

Discussion

DAI was primary diffuse brain trauma, with a high incidence, and accounted for about 50% of all severe traumatic brain injuries. In DAI, axonal structures might often be damaged because of acceleration injury-induced shear forces [1]. Meanwhile, the small blood vessels in the corresponding regions might be ruptured and bleed, and the wider the range, the worse the prognosis [2, 3]. Currently, as for DAI treatment, determining the prognosis is still difficult, and normally, patient with low GCS and bleeding sites in midline would exhibit severe clinical symptoms and poor prognoses [4-8], and their mortality accounted for 35% of the patients who died of brain trauma. It was found that 66% of the patients who died within the first day after brain trauma had pathological changes of DAI. There is no effective treatment currently, and the treatment for this type of brain injury has attracted more and more attention clinically.

The concept of DAI was first proposed in the mid-1980s and referred to different-degree extensive axonal injuries in multiple cerebral sites caused by brain trauma. It was suggested that patients with continuous coma after brain injury for more than 6 h, whose CT scans were normal or exhibited punctiform high density shadows, or exhibited no significant intracranial space-occupying lesions, could be diagnosed as DAI [12]. In this study, the shortest continuous coma duration after injury was 12 hours, and none of the cases exhibited any significant space-occupying lesions in the CT scanning images, with the midline lying in the center basically, and only 12 patients exhibited punctiform high density shadows in CT scanning (except for arachnoidal hemorrhage and brain edema) and met the diagnostic criteria. But the author believed that the reason that the patient died within 6 h after traumatic brain injury was due to other associated injuries instead of traumatic brain injury; the head CT scan showed no obvious intracranial space-occupying lesions, the GCS was < 6 points, and the patient also had significant brainstem injuries, which were also classified as DAI. But the diagnosis of DAI needs to be distinguished from traumatic DBE. Traumatic DBE is caused by the increased cerebral blood flow, which is the result of trauma-caused secondary cerebrovascular autoregulation dysfunction.

GCS could be used as a simple indicator of traumatic brain injury and prognosis judgment, which is still suitable for DAI patients. From **Tables 1** and **2**, we know that the GCSs of the three groups had significant correlations with their prognoses. Furthermore, coma duration was also closely related to the prognosis, and the longer the coma, the worse the prognosis. The most significant clinical feature of the DAI patients was the long-term coma (with persistency) after injury, which was not caused by brain herniation, but the result of widespread axonal injury and a fracture-caused extensive inhibition of the upstream activation system and cortex. Adams [12] divided DAI into three levels, Level I: microscopy revealed retracted axonal balls in wide brain areas, including corpus callosum, cerebellar peduncle, and brain stem, etc.; level II: in addition to the features of level I, there were punctiform contusions in the subcortical corpus callosum, cerebellar peduncle, etc.; level III: In addition to the features of level II, punctiform contusions and bleeding foci appeared in brainstem. In this group, the severe group (24 patients), 12 patients had

brain stem symptoms, and this is consistent with pathological level III, so it could explain why the severe patients had more brainstem symptoms clinically.

Studies have shown that DAI patients do not show any characteristic changes in CT scanning [6, 8, 9] that existed when their brain tissue was tearing and bleeding, and CT could exhibit a punctiform high density shadow, so the pathological level I would exhibit normal CT scanning results, but the patients in levels II and III or with clinical moderate or severe symptoms would only exhibit punctiform high density shadows in different brain regions in high-resolution CT; therefore, a punctiform high density shadow is not a specific positive indicator for clinical diagnosis. In this study, only 1 patient in the mild group exhibited abnormal CT images within 6 h after injury (light bleeding in the arachnoid); the moderate group had 2 cases, and the severe group had 12 cases, indicating that early CT scanning after injury did not show a high positive rate. (But those in the severe group showed abnormalities in the 24-h review). Therefore, the symptom of continuous coma for more than 6 h after injury, and normal CT scanning could be used as powerful evidence in diagnosing DAI.

We still lack an effective treatment for DAI. As for DAI salvage therapy, through a retrospective summary, this study considered that the key to improving efficacy was to adopt comprehensive treatment. Modern research has shown that [9-14] only a small proportion of axonotmesis cases were caused by trauma-caused immediate shear forces, and the subsequent emergence of axonal retraction balls were the result of a series of pathophysiological changes after axonal injuries. In the early stages, the permeability of the axonal membrane was increased, and a large calcium influx was an important pathological process which could result in the deposit of a large amount of calcium intracellularly and cause the death and apoptosis of a large number of cells. The clinical treatment to this end should be more efficacious. The 36 patients in this study were given (early) calcium antagonists, but it should be noted that their blood pressure should not be reduced too much. Early hypotension and hypoxemia are the main reasons for the increased mortality and disability of DAI patients; therefore, an early tracheotomy, if necessary, and a ventilator could be used, is the key to improving the survival rate of patients with severe DAI, which could maintain airway patency, reduce respiratory failure-resulted death, and provide effective protections to cooling and cerebral protection. Meanwhile, the internal environment should be kept stable, and the imbalance of blood-gas, blood sugar, water and electrolytes should be corrected, complications should be prevented, and nutritional support is also necessary. The patient with SAH should undergo a lumbar puncture to release bloody cerebrospinal fluid to adequately increase blood pressure and to maintain cerebral perfusion pressure. Secondly, the sites and circumstances of injuries should be quickly determined according to CT or MRI findings to determine whether emergency surgery should be done or not. The patients that need no surgery should have their intracranial pressure reduced, in order to maintain stable vital signs and internal environments. Meanwhile, patients should undergo sub-hypothermia treatment as soon as possible, in order to reduce brain oxygen consumption, increase the tolerance of the central nervous system to hypoxia, reduce cerebral edema, and increase intracranial pressure [5, 6]. The awareness of DAI patients is unclear, and because they cannot eat, with more complications, nutritional support treatment should be given to prevent and treat complications. Patients should also carry out early physical exercise to strengthen their bodies and reduce the rates of morbidity and disability. Hyperbaric oxygen therapy could be performed to promote the recovery of nerve cells, reduce cerebral edema, improve microcirculation, and increase blood supply towards the lesion area. Hyperbaric oxygen therapy also allows improvements in the reticular activating system and brainstem functions, thus improving the metabolism of the brain cells, 3) the application of naloxone could inhibit the secretion of B-endorphin, deplete opioid receptors, thus avoiding opioid peptide-increasing caused secondary brain damage, especially towards DAI-caused coma and respiratory depression, naloxone could quickly reverse the unconsciousness, release respiratory depression nerve growth factor, and naloxone could promote the recovery of brain functions, and help the comatose patients wake up; thus, it would have significant impacts on prognosis [15-20]. In short, DAI should be dealt with cor-

rectly and effectively, and an early correct diagnosis and comprehensive treatment measures are the keys to reduce the rates of mortality and disability, as well as to obtain a good prognosis.

Disclosure of conflict of interest

None.

Address correspondence to: Lin Dan, Department of Neurosurgery, Tonglu First People's Hospital, Xueshen Road, Tonglu, Hangzhou 311500, Zhejiang Province, China. E-mail: 22414396@qq.com

References

[1] Buki A and Povlishock JT. All roads lead to disconnection? Traumatic axonal injury revisited. Acta Neurochir (Wien) 2006; 148: 181-194.

[2] Park JH, Park SW, Kang SH, Nam TK, Min BK and Hwang SN. Detection of traumatic cerebral microbleeds by susceptibility-weighted image of MRI. J Korean Neuosurg Soc 2009; 46: 365-369.

[3] Barnes SR and Haacke EM. Susceptibility-weighted image: clinical angiographic applications. Magn Reson Imaging Clin Nam 2009; 17: 47-61.

[4] Tong KA, Ashwal S, Holshouser BA, Nickerson JP, Wall CJ, Shutter LA, Osterdock RJ, Haacke EM and Kido D. Diffuse axonal injury in children: clinical correlation with hemorrhagic lesions. Ann Neuol 2004; 56: 36-50.

[5] Maxwell WL, Mackinnon MA, Stewart JE and Graham DI. Stereology of cerebral cortex after traumatic brain injury matched to be Glagow coma score. Brain 2010; 133: 139-160.

[6] Park SJ, Hur JW, Kwon KY, Rhee JJ, Lee JW and Lee HK. Time to recover consciousness in patients with diffuse axonal injury: assessment with reference to magnetic resonance gradind. J Korean Neurosurg Soc 2009; 46: 205-209.

[7] Jang SH, Kim SH, Kim OL, Byun WM and Ahn SH. Corticospinal tract injury in study. Neurorehabilitation 2009; 25: 229-233.

[8] Hergan K, Schaefer PW, Sorensen AG, Gonzalez RG and Huisman TA. Diffuse weighted in diffuse axonal injury of the brain. Eur Radiol 2002; 12: 2536-2641.

[9] Gobbel GT, Kondziolka D, Fellows-Mayle W and Uram M. Cellular transplantation for the nervous system: impact of time after preparation on cell viability and survival laboratory investigation. J Neurosurg 2010; 1: 666-672.

[10] Sun X, Wang X, Chen TX, Li T, Cao K, Lu A, Chen Y, Sun D, Luo J, Fan J, Young W and Ren Y. Myelin activates FAK/Akt/NF-KB pathways and provokes CR3-dependent inflammatory response in murine system. PLoS One 2010; 5: 9380-9385.

[11] Smith DH, Meaney DF and Shull WH. Diffuse axonal injury in head trauma. J Head Trauma Rehabil 2012; 18: 307-315.

[12] Adams JH, Doyle D, Ford I, Gennarelli TA, Graham DI and McLellan DR. Diffuse axonal injury: definition, diagnosis and granding. Histopathology 1989; 15: 49-59.

[13] Kumar R, Husain M, Gupta RK, Hasan KM, Haris M, Agarwal AK, Pandey CM and Narayana PA. Serial changes in the white matter diffusion tensor imaging metrics in moderate traumatic brain injury and correlation with neurocognitive function. J Neurotrauma 2009; 26: 481-495.

[14] Skandsen T, Kvistad KA and Solheim O. Strand IH prevalence and impact of diffuse axonal injury in patients with moderate and severe head injury: acohort study of early magnetic resonance imaging findings and 1-year outcome. Neurosurg 2010; 1: 556-663.

[15] Li XJ. The image analyzing computer of DAI. Chinese J Clin Neurosurg 2008; 12: 543-544.

[16] Povlishock JT and Kalz DI. Update of neuropathology and neuro-logical recovery after traumatic brain injury. J Head Trauma Rehabil 2005; 20: 76-94.

[17] Nair JR, Van Hecke W, De Belder F, Venstermans C, van den Hauwe L, Van Goethem J and Parizel PM. High-resolution susceptibility-Weighted imaging at 3 T with a 32-channel head coil: technique and clinical applications. AJR Am J Roentgenol 2013; 195: 1007-1014.

[18] Linfante I, Llinas RH, Caplan LR and Warach S. CT features of intracerebral hemorrhage within 2 hours from symptom onset. Stroke 2012; 30: 2263-2269.

[19] Tong KA, Ashwal S, Holshouser BA, Shutter LA, Herigault G, Haacke EM and Kido DK. Hemorrhagic shearing lesions in children and adolescents with posttraumatic diffuse axonal injury: improved detection and initial results. Radiology 2013; 227: 332-337.

[20] Guan GL, Huang ZX and Lin QM. The protective effect of naloxone on nerve function in head trauma. Chinese J Clin Neurosurg 2013; 20: 571-572.