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Diffuse axonal injury (DAI) in moderate to severe head injured patients: Pure DAI vs. non-pure DAI

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ABSTRACT

Objective: Diffuse axonal injury (DAI) is known to be associated with poor outcome. DAI often associates with other intracranial injuries but their distinct features have not been established. In this retrospective cohort study, we compared clinical outcomes between pure and non-pure DAI patients.
Patients and Methods: Total of 1047 traumatic brain injury (TBI) patients visited our institute between 2011 and 2017. Age ranged between 15–85 years old and Glasgow coma scale (GCS) score less than 13 were included. DAI was diagnosed in 45 patients using CT and MRI and their clinical features and outcomes were compared depending on their associated cranial injury; 20 patients without evidence of associated injury (Pure DAI group) and other 25 patients with associated injury (Non-pure DAI group). DAI stage was adopted using Gentry, L.R. classification. Glasgow outcome scale (GOS) was measured at least 6 months after trauma to evaluate their functional outcome.
Results: The mean age and follow-up period were 45.36 years and 15.09 months, respectively. There were no significant differences between pure and non-pure DAI groups regarding demographic data and clinical findings on their admission. Logistic regression model was used to examine the association between GOS and clinical factors. In this analysis, pure DAI was no significantly different to non-pure DAI ($p = 0.607$). However, DAI Stage, transfusion, and hypotension on admission were strongly related to poor outcome. Stage III showed sevenfold higher risk when compared to Stage I ($p = 0.010$). The risk was also high when Stage III was compare to Stage I and II ($p = 0.002$). Interestingly, no significant difference was observed between Stage I and II ($p = 0.847$).
Conclusions: Unfavorable outcome was observed in 14 patients (31.11%) which was lower than we expected. Interestingly, non-pure DAI was no worse than pure DAI on their functional outcome. However, DAI Stage III was independently associated with poor outcome when compared to Stage I or I and II. Finally, we concluded that Stage II is clinically more related to Stage I, rather than Stage III.

1. Introduction

Moderate to severe traumatic brain injury (TBI) is a major cause of death and disability [1]. Despite its significant social concerns, the outcome prognosis for TBI is challenging in part owing to its heterogeneous pathology and complexity [2]. Generally, TBI may be classified according to its neuro-radiological and biomechanical features: focal (fracture, contusion, subdural hematoma [SDH] or epidural hematoma [EDH]) or diffuse (diffuse brain edema and diffuse axonal injury [DAI]) [1]. Among these injuries, DAI is considered as one of the main causes for loss of consciousness in post-traumatic cases with the absence of detectable intracranial lesions on computed tomography (CT) [3].

The mechanism of DAI is a stretching and deformation of the brain tissue caused by angular or rotational acceleration-deceleration on different axes leading to direct damage of blood vessels and axons [4]. This phenomenon is often present in severe TBI patients [5,6], and comparing to focal injury, it seems to be more important predictor of poor functional outcome and cognitive impairments [7–9].

The histopathological grading of DAI was suggested by Adams and colleagues in 1989 [10]. They classified grades from 1 to 3 depending

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on the presence of axonal injury: in the cerebral hemispheres with a predilection for the grey-white interface (Grade 1), the corpus callosum (Grade 2), and the dorsolateral or rostral brainstem (Grade 3). Patients with severe TBI were more likely to have higher DAI grades with associated cranial injuries [11]. This finding is in accordance with Ommaya AK model [12]; consecutive involvement of more deeper and central brain structures as the load of traumatic impact increases.

DAI was considered as the pathological indication of many post-traumatic neurological deficits, and hence described as a poor prognostic sign. Some reported worse outcomes of DAI with 40–87.5% of disability and 20–41% of dependency evaluated with Glasgow outcome scale (GOS) or Glasgow outcome scale extended (GOSE) [13–15]. However, most of these studies were the result of non-pure DAI, defined as DAI with other associated brain injuries, such as traumatic-subarachnoid hemorrhage (T-SAH), intraventricular hemorrhage (IVH), intracerebral hemorrhage (ICH), SDH, EDH and much more. In fact, we believe that these associated injuries may be the confounding factors disorienting patient's prognosis and obscuring the analysis for the outcome of pure DAI patients. It is a matter of logical belief that the clinical impact of non-pure DAI will be much worse compare to pure DAI. However, the clinical impact of these 2 injuries have never been compared and investigated together. Accordingly, to determine the prognosis and outcome of DAI more effectively, these injuries must be involved with their distinct features. To our knowledge, the concept of pure vs. non-pure DAI has not been elucidated in current clinical practice.

The objective of this study was to examine and summarize the clinical difference between pure and non-pure DAI in moderate to severe TBI patients. In addition, we verified some clinical factors that were associated with functional outcome, as measured with GOS.

2. Materials and methods

2.1. Patient population

Following Institutional Review Board approval, we retrospectively reviewed a cohort of 1047 patients admitted to our hospital for acute head trauma between January 2011 and April 2017. The patient age ranged between 15–85 years old were included. The diagnosis of traumatic DAI was confirmed using cranial CT scan or magnetic resonance imaging (MRI) by certified neuro-radiologists. DAI and associated injuries observed on CT scan were classified according to Marshall classification [16]. Non-pure DAI patients were excluded if associated cranial injuries lead to a high risk of mortality and hence confounding our analysis. These include patients with Marshall's classification grade III and IV. TBI patients were evaluated upon admission by clinicians using various types of scoring systems; Glasgow coma scale (GCS) [17], injury severity score (ISS) [18], and revised trauma score (RTS) [19]. The patient was excluded if the GCS on admission was above 14. Also, in cases where GCS was falsely low due to non-head trauma, like alcohol intoxication or major non-head traumas [20], patients were excluded too.

2.2. Demographic and injury related factors

We involved demographic factors like age, sex, and medical comorbidities (hypertension, diabetes mellitus, asthma and etc.). The injury mechanisms were motor vehicle accident, pedestrian accident and fall. The scoring systems (GCS, ISS, and RTS), vital signs (mean arterial pressure, heart rate, respiratory rate, and body temperature), and laboratory data (arterial blood gas analysis [ABGA], hemoglobin, hematocrit, white blood cell [WBC], platelet, prothrombin time [PT], sodium, glucose, blood urea nitrogen [BUN], creatinine, c-reactive protein [CRP], and lactic acid) that reflected the severity of trauma upon admission were analyzed. Also factors like transfusion within 24 h of visit, administration of sedative drugs (propofol or remifentanil), mannitol for increased intracranial pressure (ICP), follow up interval (months), days of hospital stay, ICU stay, and ventilation care were thoroughly reviewed.

2.3. Radiologic analysis – cranial CT and MRI

Cranial CT was performed in all patients on their admission. MRI was not routinely performed, but it was recommended when CT scan could not clearly give account of patient's decreased consciousness or when patient's level of consciousness did not match CT findings. In our institution, we obtained MR images using T1, T2-weighted, fluid attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequences in axial, sagittal, and coronal planes. Some MRI sequences that are sensitive to hemorrhagic lesions such as susceptibility-weighted imaging (SWI) or T2-weighted gradient echo (T2 GRE) were not routinely performed. We analyzed anatomical location of DAI lesions (subcortical white matter, cerebellum, internal capsule, basal ganglia, thalamus, corpus callosum, and brainstem) and number of DAI lesions (categorized into 1–3, 4–6, 7–9, and more than 10 lesions). Non-pure DAI was defined as any evidence of associated traumatic injuries (T-SAH, IVH, ICH, SDH, and EDH) observed on CT or MRI. Multiple selections were available for DAI lesions and associated traumatic injuries.

DAI stage was directed according to Gentry, L.R. classification [5], depending on the presence of axonal injury in different anatomical locations; if DAI lesion was confined to lobar white matter (Stage I), the corpus callosum (Stage II), or brainstem (Stage III) (Fig. 2). This staging was adapted for each sequence separately and for all MRI sequences combined. It was marked according to the highest stage given for any sequence.

2.4. Neuro-intensive care managements

TBI patients with unstable hemodynamic status or decreased level of consciousness were initially admitted to ICU. These patients were managed according to a standard guideline of ICU for cerebral perfusion pressure and ICP [21]; 30° elevated head of bed, hyperventilation (target PCO2 30–35 mmHg) and a central venous pressure (target 0–5 mmHg). The mean arterial pressure was managed above 70 mmHg. Generally, transfusion was guided to maintain within a normal range; hemoglobin > 9 g/dL, PT > 50%, and platelets > 100,000 g/L. The patient was intubated if there was evidence of decreased level of consciousness (GCS score < 8) or respiratory distress. Mannitol was administrated in cases where cerebral edema was observed on CT or MRI scans. Surgery was considered when a decreased level of consciousness or worsened radiologic findings were observed despite the best medical treatment.

2.5. Clinical outcome assessment

TBI patients were assessed using GOS system at least 6 months after the trauma for their functional outcome. This system classified patients into 5 groups with increasing severity ranging from good recovery to death [22]. In our study, these outcomes were dichotomized into favorable (GOS 3, 4, and 5) and unfavorable (GOS 1 and 2) groups for more efficient analysis. There were no survival patients lost to follow-up.

2.6. Statistical analysis

A statistical analysis was performed with SPSS (version 21; SPSS Inc., Chicago, IL, USA). The statistical significance was tested using a standard chi-square test or Fisher's exact test for categorical variables, and Student's *t*-test or Kruskal-Wallis test for continuous variables. The relationship between DAI and clinical outcome was analyzed using univariate logistic regression models. All factors identified by a