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Research report

Early stage alterations of catecholamine and adrenocorticotropic hormone levels in posttraumatic acute diffuse brain swelling

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ABSTRACT

Posttraumatic acute diffuse brain swelling (PADBS) is characterized by serious brain bulk enlargement rapidly following trauma and is a major cause of elevated intracranial pressure and thus mortality. The pathogenesis of PADBS is not clearly understood, and the early stage alterations of catecholamine (CA) and adrenocorticotropic hormone (ACTH) levels in PADBS also remain largely unknown. The objective of this study was to investigate CA and ACTH levels in the patients with PADBS in the early stage and discuss the possible roles CA and ACTH in the pathogenesis of PADBS. It is a cross-sectional study. A group of patients with PADBS (n = 10) was compared with a group of patients with severe brain injury (SBI) (n = 33). A control group of healthy adults (n = 25) was also included. Blood samples were obtained to measure levels of epinephrine (EPI), norepinephrine (NE), dopamine (DA), and ACTH as soon as the patients arrived at the neurosurgery department, which was done within 4 h after trauma. Both SBI and PADBS groups of patients had higher levels of EPI, NE, DA, and ACTH than the control group. The PADBS group had significantly higher levels of EPI, NE, and ACTH than the SBI group. CA and ACTH levels are significantly increased in early stage PADBS. These results imply that CA and ACTH may play important roles in the pathogenesis of PADBS. To eliminate the effects of CA and ACTH at the early stage, and thereby protect the hypothalamus and brain stem, might be critical measures for treating patients with PADBS.

1. Introduction

Considerable mortality and morbidity, particularly in young people, is attributable to severe head injury in Western countries (Farin et al., 2003). Mortality and severe disability are strongly associated with an increase in intracranial pressure (ICP) (Eker et al., 1998). When increased ICP cannot be controlled brain swelling occurs and the prognosis becomes very poor (Jiang et al., 2014). In patients with traumatic brain injury, intraoperative severe brain swelling has been associated with decompressive surgical procedures to evacuate a supratentorial intradural mass lesion (Wang et al., 2013). The pathophysiological mechanism of posttraumatic brain swelling is not well understood (Jiang et al., 2014) although there have been many studies aimed at clarifying the mechanism (Lobato et al., 1988; Yoshino et al., 1985).

It is relatively widely believed (Crompton, 1971; Sangiorgi et al., 2013; Snoek et al., 1979; Yoshino et al., 1985) that the rapid development of swelling is due to vascular engorgement, which was first proposed by Langfitt et al. in the 1960s (Langfitt et al., 1966). The impact of trauma can cause severe diffuse brain damage. As a consequence, vasomotor paralysis is triggered because the hypothalamus and brain stem, which are vasomotor centers (Nagao et al., 1986), are frequently involved in severe diffuse brain injury. Vasomotor paralysis causes a sudden increase in cerebral blood flow and volume. This results in dramatic brain bulk enlargement which leads to a severe increase in ICP, decrease in cerebral perfusion pressure, and obstruction of the venous outflow mechanisms. Wu et al. (1998) successfully established an experimental rabbit model of acute diffuse brain swelling after electrolytic destruction of the

Abbreviations: ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin; CA, catecholamine; CNS, central nervous system; CT, computed tomography (CT); DA, dopamine; EPI, epinephrine; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; HPA, hypothalamus-pituitary-adrenocortical; ICP, intracranial pressure; IQR, inter-quartile range; MODS, multi-organ dysfunction syndrome; NE, norepinephrine; PADBS, posttraumatic acute diffuse brain swelling; SBI, severe brain injury.

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dorsomedial nucleus of the hypothalamus, the midbrain reticular formation, and/or the reticular formation of the medulla oblongata. However, the precise mechanism of the injury to the hypothalamus and brain stem leading to an increase in cerebral blood flow and brain swelling is still poorly understood, and little has been done to investigate the changes of neurotransmitters related to this process.

Measurement of brain water content in patients with head injuries (Clifton et al., 1980; Sioutos et al., 1995) have demonstrated that posttraumatic brain edema may occur much more rapidly than is usually thought. Densitometric and dynamic CT studies (Lanksch et al., 1981; Yoshino et al., 1985) seem to indicate that acute edema formation is the most likely cause of bulk brain enlargement in cases of fatal head injury. Nevertheless, the neurochemical mechanisms of acute edema are not yet understood. It has been reported that dopamine (DA) may be related to increased edema (Pfister et al., 2008). On the other hand, there is evidence that norepinephine (NE) may play a protective role, possibly by stabilizing the blood–brain barrier in areas of the brain next to the site of injury (Dunn-Meynell et al., 1998).

It has been demonstrated that trauma initiates a cascade of physiological processes (Marik and Flemmer, 2012; Rohleder and Karl, 2006). Hinson and Sheth (2012) have reviewed the literature on autonomic dysfunction after traumatic brain injury. Fear and pain accompanied by trauma act as powerful provokers of the sympathoadrendal axis and hypothalamus-pituitary-adrenocortical (HPA) axis, which results in increased changes of sympathetic tone, and release of adrenocorticotropic hormone (ACTH) and catecholamines (CA), including epinephrine (EPI), NE, and DA, which have numerous effects on blood pressure, heart rate, heart contractibility, and ventilation rate. Although these effects after severe injuries may increase survival probability in the short term, strong, long-term excitation of the sympathoadrendal axis and HPA axis can lead to reverse physiological effects. High levels of ACTH and CA cause serious arteriolar contraction and metabolic substrate toward to peripheral tissues which is seen in severe trauma.

Despite the abundant evidence that damage to the hypothalamus and brain stem is involved in the pathogenesis of posttraumatic acute diffuse brain swelling (PADBS), the changes in CA and ACTH still need to be determined. Catecholamines and ACTH are greatly increased at the early stage in patients with PADBS in which the hypothalamus and brain stem, as vasomotor centers, are triggered. This increase in CA and ACTH is associated with a sudden increase in cerebral blood flow and consequently rapid brain bulk enlargement. With regard to a possible mechanism, soon after trauma, CA secreted in the hypothalamus and brain stem locus coeruleus may activate β-adrenoreceptors and subsequently dilate cerebral vessels (observed in animal model). Then the secretion of CA increases, and CA further activates α-adrenoreceptors, leading to the intense constriction of cerebral vessels, especially the vessels in the outflow tract, resulting in severe brain swelling and brain ischemia.

Based on various studies, it appears that CA and ACTH may play important roles in the pathogenesis of PADBS, and eliminating the effects of CA and ACTH at the early stage could be critical for the treatment of patients with PADBS. The aim of this study was to investigate CA and ACTH levels during the early stage of PADBS to increase understanding of the pathogenesis of PADBS.

2. Materials and methods

This study was approved by the local research ethics committee, and written informed assent was obtained from the next of kin of all patients.

From 98 patients admitted to the emergency service of Shantou University Medical College between June 2012 and December 2012 a total of 10 patients with PADBS were selected for this cross-sectional, descriptive, analytic study. The 10 patients did not sustain any severe injury other than head injury, and all were in good health before suffering head injury. These patients did not receive any therapy or other form of management prior to admission and were transferred directly to our hospital from the scene of the accident. Blood samples were obtained to measure CA and ACTH levels as soon as the patients arrived at our neurosurgery department. Three of these patients had oxygen saturation lower than 90% on admission. Oxygen was administered via mask to 2 patients and intratracheal intubation was performed on the other patient. Following this management oxygen saturation returned to above 90%. It also should be noted patients were in a compensation phase for ICP soon after trauma and thus did not develop hypotension. All 10 patients were comatose as defined by the Glasgow Coma Scale (GCS) and all underwent a CT scan immediately after admission. The inclusion criteria were the following: 1) age 14–80 years; 2) coma occurred after brain trauma and patients were admitted within 4 h after trauma; 3) GCS score 3–6; 4) CT confirmed the compression of the third ventricle and basal cistern. The exclusion criteria were the following: 1) received therapy prior to admission (includes surgical and nonsurgical interventions and supportive therapy); 2) younger than 14 years or older than 80 years; 3) history of mental illness or heart disease; 4) epidural or subdural hematoma; 5) other concomitant intracranial disease. Patients were also excluded if the time interval from trauma to admission was about 4–14 h; to minimize confounding factors the time interval was limited to within 4 h.

Thirty-three patients with severe brain injury (SBI) were also included in this study. These patients had either a simple huge epidural hematoma (without brain contusion) and developed brain stem shift due to the hematoma but had no primary brain stem injury, or had diffuse axonal injury. The inclusion criteria were the following: 1) multiple non-occupying hemorrhagic foci (< 2 cm) in the white matter of the cortex, corpus callosum, and brain stem; 2) subarachnoid or intraventricular hemorrhage; 3) hemorrhagic foci adjacent to the third ventricle; 4) disease was severe but CT scan was normal.

The routine analysis of free CA was carried by using an HPLC-EC (M515 pump, Wisp 740 auto sample and a M460amperometric detector; Waters, Saint Quentin, France) (Hamill et al., 1987). Analysis of ACTH was performed by using IMMULITE (DPC Immulite 2000, Bad Nauheim, Germany) (Koiv et al., 1997). Routine serum laboratory tests included serum levels of glucose detected by automatic biochemical analyzer (Roche Modular PPI, Mannheim, Germany). Clinical examination and GCS estimation were performed every day by a neurosurgery resident. The Glasgow Outcome Scale (GOS) score was determined when patients were discharged.

A normal control group consisted of 25 healthy adults. Their mean age was 32.3 ± 14.7 years (range, 13–72 years; median, 28 years). All control subjects gave informed consent before participating in the study.

2.1. Statistical analysis

Because of the small sample size of the PADBS group, continuous data were presented as median and inter-quartile range (IQR). Differences between the three groups (PABDS, SBI, and normal control) were analyzed by the non-parametric Kruskal-Wallis test followed by the non-parametric Mann-Whitney tests for pair-wise groups. The categorical data were presented by number and percentages and their associations with the three groups were analyzed by the Fisher's exact test. Two-sided P-values < 0.05 were considered to be statistically significant. Statistical analyses were performed using IBM SPSS statistics 22.0 software (IBM Corporation, Armonk, NY).