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Review

Venous system in acute brain injury: Mechanisms of pathophysiological change and function

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ABSTRACT

Cerebral vascular injury is a major component of acute brain injury. Currently, neuroprotective strategies primarily focus on the recanalization of cerebral arteries and capillaries, and the protection of insulted neurons. Hitherto, the role of vein drainage in the pathophysiology of acute brain injury has been overlooked, due to an under appreciation of the magnitude of the impact of veins in circulation. In this review, we summarize the changes in the vein morphology and functions that are known, or likely to occur related to acute brain injury, and aim to advance the therapeutic management of acute brain injury by shifting the focus from reperfusion to another term: recirculation. Recent progress in the neurobiological understanding of the vascular neural network has demonstrated that cerebral venous systems are able to respond to acute brain injury by regulating the blood flow disharmony following brain edema, blood brain barrier disruption, ischemia, and hemorrhage. With the evidence presented in this review, future clinical management of acutely brain injured patients will expand to include the recirculation concept, establishing a harmony between arterial and venous systems, in addition to the established recanalization and reperfusion strategies.

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Case report

A 44 year-old man was transferred to the department of Neurosurgery, Zhejiang University Second Affiliated Hospital from a local hospital. He had been in a car accident about one month ago prior to his referral. The accident triggered the onset of chronic moderate headaches. His Glasgow Coma Scale was 15 at admission. Initially, computerized

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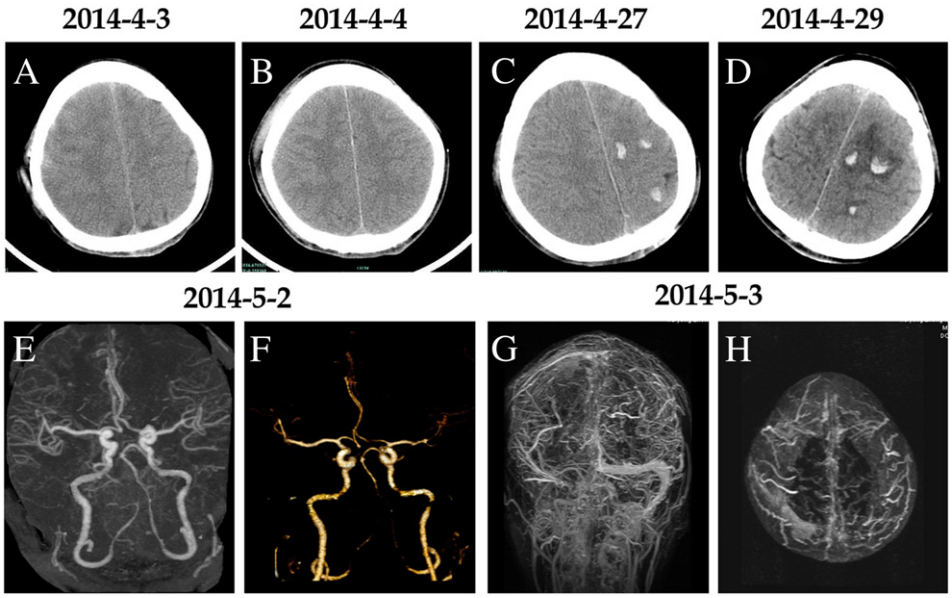

Fig. 1. Examination images of the patients. A and B: Computerized tomography scan did not reveal any abnormity in the brain at his first administration. C and D: Computerized tomography scan revealed multiple hematomas with edema in the left cerebral at his second administration. E and F: Computerized tomography angiography did not reveal aneurysms and vascular malformation. G and H: Magnetic resonance venography indicated thrombosis in superior sagittal sinus and right transverse sinus.

tomography (CT) scan did not reveal any abnormality in his brain (Figs. 1A and B). The values of his D-Dimer, prothrombin time, and activated partial thromboplastin time were 3100 μg/L FEU↑, 12 s and 30.5 s, respectively. One week later, after conservative treatment with mannitol and an antifibrinolytic agent, his headache resolved, and he was discharged. Two weeks later, he was readmitted with more severe headaches, limb twitching, staring gaze, trismus and foaming of the mouth. His Glasgow Coma Scale was 11 this time. Emergency CT scan showed that multiple fresh small hematomas had developed in the left parietal lobe surrounded by severe brain edema (Figs. 1C and D), which was different from the primary hematoma. No aneurysm or arteriovenous malformation was detected by computerized tomography angiography (CTA) (Figs. 1E and F), but magnetic resonance venography (MRV) indicated thrombosis in superior sagittal sinus, right sigmoid sinus, and right transverse sinus (Figs. 1G and H). The values of his D-Dimer, prothrombin time, and activated partial thromboplastin times were respectively 5590 μg/L FEU↑, 13.5 s and 26.7 s, indicating that he suffered from hypercoagulability. Subsequently, he left the hospital with paralysis of both right limbs.

This case raises important questions: Why did the patient re-bleed in a non-traumatized area long after the incident? Can acute brain injury impair the cerebral venous system? How do venous system lesions exacerbate acute brain injury? This case highlights the fact that acute brain injury may lead to pathologic changes in cerebral venous system, which demonstrates the value of including vein evaluation in the diagnostic workup of central nervous system disorders and the importance of identifying possible causes that could be reversed with appropriate treatment.

Introduction

Neuroprotective strategies that target attenuation of dysfunction and insult on neuronal cells but do not address vascular injury, fail to exhibit greater beneficial effects on acute central nervous system injuries, including stroke, traumatic brain injury and spinal cord injury (Seifert and Pennypacker, 2014; Silva et al., 2014; Xiong et al., 2014). Cerebral vascular injury is a major component of acute brain injury. Ischemic stroke, subarachnoid hemorrhage, intracerebral hemorrhage, and traumatic brain injury all result in either immediate or later reduction in cerebral blood flow (Ohkuma et al., 2000; Schwarzmaier et al., 2010). Therefore, the discovery of the "neurovascular unit" advocates that more attention should be given to the role of vascular cells in pathological processes of acute brain injury (Lo and Rosenberg, 2009; Tso and Macdonald, 2014). The neurovascular unit is comprised of endothelial vascular cells, pericytes, vascular smooth muscle cells, glial cells (e.g. astrocytes, microglia and oligodendroglia), and neurons. However, the neurovascular unit focuses on the significance of capillaries and the cells directly attached around capillaries, but does not contain the upstream arteries/arterioles and downstream veins/venules. Arteries and veins play vital roles in the control of vascular tone and blood supply, and have influence on downstream capillaries, and blood drainage. Therefore, we recently proposed a new concept of a vascular neural network, which is a more comprehensive pathophysiological model of acute brain injury than the neurovascular unit, comprising all of the cells and structures that are required to maintain cerebral blood flow under physiological and pathological conditions (Zhang et al., 2012a). To some extent, the vascular neural network is a concept that partially spawned from Chinese medicine "Huo-Xue-Hua-Yu", which suggested a treatment strategy to maintain arterial and venous blood flow harmony during circulation for acute central nervous system disorders (Leak et al., 2014; Li et al., 2014). In clinical management, the role of vein drainage in the pathophysiology of acute brain injury is often overlooked due to the dearth of information about the impact of veins in circulation and incomplete characterization of them.

In this review, we summarize the changes in the vein morphology and function that are known, or likely to occur related to acute brain injury, and aim to move forward from the goal of reperfusion to a therapeutic strategy incorporating vasculature homeostasis in acute brain injury.

General anatomy and physiology of the cerebral venous system

The brain receives up to 20% of cardiac output. The entire normal cerebral circulation contains large arteries, arterioles, capillaries, and downstream venules, and veins. The vascular circulation is divided in two categories: extraparenchymal and intraparenchymal cerebral blood vessels. Extraparenchymal vessels include the main feeding arteries, pial blood vessels, and penetrating blood vessels. The penetrating arteries enter the brain parenchyma, surrounding by the Virchow Robin space with cerebrospinal fluid, and their tone is controlled by