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Case Report

Iron Deposit- The Potential Pathogenesis in Central Post-Stroke Pain?

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Abstract

Background and Purpose: The etiology of central post-stroke pain (CPSP) is poorly understood and such pains are often refractory to therapy. To explore the pathophysiology of such pain in thalamic hemorrhage, we compared 2 patients with CPSP to 1 without CPSP by magnetic resonance imaging (MRI).

Methods: We experienced 2 patients, who, following hemorrhage of thalamic region, suffered from an insufferable and inexpressible pain, this was accompanied with hemi-anaesthesia. A year later, *MRI* has been used to compare with another 1 similar cases without CPSP after thalamic hemorrhage.

Results: MRI showed that low signal intensity on T2-weighted images near to thalamic region in CPSP, while high intensity displayed in similar position without CPSP.

Conclusions: we speculate iron (ferritin or hemosiderin) may take part in the theories of central pain generation.

ABBREVIATIONS

CPSP: Central Post-Stroke Pain; ICH: Intra Cerebral Hemorrhage; CT: Computerized Tomography; MRI: Magnetic Resonance Image; SWI: Susceptibility-Weighted Imaging

INTRODUCTION

Central Post Stroke Pain (CPSP) refers to pain resulting from a primary lesion or dysfunction of the central nervous system after a stroke. The etiology and pathophysiology of CPSP is the least recognized and poorly understood, there are few evidence-based effective treatment strategies for such pain. No data have been reported that iron may play a role in pathophysiology of CPSP. Here we reported 2 cases with CPSP probably caused by iron deposit around thalamus.

CASE PRESENTATION

3 patients with thalamic hemorrhage were recruited from hemorrhagic stroke inpatient. The research was approved by the Second Hospital of Shanxi Medical University Ethics Committees, and all participating patients signed an informed consent form. The description of this study is to observe and comparative analyze their head MRI for 1 year following intracerebral hemorrhage (ICH).

Case 1 A right-handed 58-year-old female, initially attack at the age of 57, was a primary school teacher, with left hemi-anaesthesia and insensitive to pain followed by a right thalamic hemorrhage. Her computerized tomography (CT) scan on admission showed "*an area of high density related to the right thalamus, which most likely represents recent hemorrhage*" (Figure 1a). She had a history of diabetes mellitus for 20 years and treated with insulin for 2 years, she also had a history of hypertension for 10 years without medication, but no history of stroke or psychiatric illness. Her past medical history included a right breast proliferation which had been resected and myoma of uterus. She did not undergo surgical intervention because the hematoma was small. In the following days, She was treated for hypertension and the majority of hematomas subsided but was gradually replaced (from month 2 onwards) by left hemi-body pain. She described having continuous "swollen and dull" and intermittent "burning or ice cold" on the whole of the left side of her body and such severe tactile allodynia that she had hardly tolerate any touch or movement. Her left hand always posed patulous and cannot touch anything, the fingers seemed swollen and ashine, the knuckle's rumple lessened. At that time, she had mild left hemiparesis but no headache, dizziness and hemianopia. 1 year after her intracerebral hemorrhage (ICH), the aforementioned symptoms of sensory were exacerbated further. Tactile allodynia was still a prominent feature and she complained of consequent difficulties with normal human contact. Her CT scan again indicated the hematoma vanished (Figure 1b).

Case 2 A right-handed 68-year-old male, initially attack at the age of 67, was a retired technicist, with left hemi-anaesthesia and insensitive to pain followed by a right thalamic hemorrhage. His computerized tomography scan on admission showed "*an area of high density related to the right thalamus*" (Figure 2a). He had a history of diabetes mellitus for 8 years and hypertension for 10 years with medication, but no other illness. He was gradually replaced (from month 2.5 onwards) by left hemi-body stiffness and pain.

Case 3 A right-handed 72-year-old male, initially attack at the age of 71, was a retired worker, with right hemi-anaesthesia and insensitive to pain followed by a left thalamic hemorrhage. His computerized tomography scan on admission showed "*an area of high density related to intraventricular and the left thalamus*" (Figure 3a). He had a history of hypertension for 30 years with medication, but no other illness. The right hemi-anaesthesia was alleviated from 1 month after ICH. Reexamination of skull CT showed hematoma disappeared in a year after ICH (Figure 1b, 2b, 3b). Head MRI of Cases 1 and 2 showed that low signal intensity on T2-weighted phases near to thalamic region (Figure 1c, 2c), SWI phases of case 2 displayed a large low signal around lesions (Figure 2d); Meanwhile on T2-weighted phases showed a high intensity at original lesions in Cases 3 by head MRI (Figure 3c).

DISCUSSION

Central post-stroke pain (CPSP) is a neuropathic pain syndrome that can occur after a cerebrovascular accident. This syndrome is characterized by pain and sensory abnormalities in the body parts that correspond to the brain territory that has been injured by the cerebrovascular lesion [1]. CPSP patients present with diverse sensory symptoms and its etiology and pathophysiology is still poorly understood [1].

Several studies have shown that hemoglobin and its degradation products, in particular iron, resulting from erythrocyte lysis after ICH exert neurotoxic effects and contribute to the development and progression of brain edema following ICH and that treatment with iron chelators can reduce these effects [2,3]. The diagnosis of ICH was established by CT. Iron neurotoxicity has been linked to delayed neuronal injury and edema formation after ICH [2,3].

Magnetic resonance imaging (MRI) is a valuable assessment tool with its unique specificity to hemoglobin degradation products and iron. Iron deposition in the brain can be detected with MRI [2,4]. The iron atoms form ferric oxyhydroxide particles, which shorten the relaxation times on T_2-weighted images resulting in darker (hypointense) signal in brain regions with higher iron content [2,5]. Signal intensity on T_2-weighted images has been used to reflect the regional iron deposition of brain tissue in normal aging and neurodegenerative conditions associated with pathological disturbance of brain iron homeostasis [2,4,5]. T2 shortening can also be produced by ferritin and hemosiderin [5,6]. The amount of iron deposition in the brain may serve as a surrogate biomarker for different ICH lesion characteristics.

Susceptibility-weighted imaging (SWI) is a new means to enhance contrast in MR imaging, which uses tissue magnetic susceptibility differences to generate a unique contrast, different from that of spin density, T1, T2, and T2*. The use of SWI filtered phase as a means to visualize and potentially quantify iron in the brain is presented [7,8]. SWI offers information about any tissue that has a different susceptibility than its surrounding structures such as deoxygenated blood, hemosiderin, ferritin, and calcium [6,7,9]. SWI filtered-phase images have been shown to be useful for observing increased iron content in the brain. New reports showed that using SWI to quantify the iron deposition is a useful tool in healthy and unhealthy subjects [10,11].

In general, the appearance of intracranial hemorrhage at MRI depends primarily on the age of the hematoma and the type of MR contrast. As a hematoma ages, the hemoglobin passes through several forms (oxyhemoglobin, deoxyhemoglobin, and methemoglobin) prior to red cell lysis and breakdown into ferritin and hemosiderin [6,12]. The MR appearance depends on the form of hemoglobin present and on whether hemolysis has occurred. The stages of hemorrhage distinguishable by MR imaging are: hyperacute (less than 1 day, intracellular oxyhemoglobin, long T1 and T2), acute (1-7 day, intracellular deoxyhemoglobin, long T1, short T2), subacute (7-14 days, intracellular and extracellular

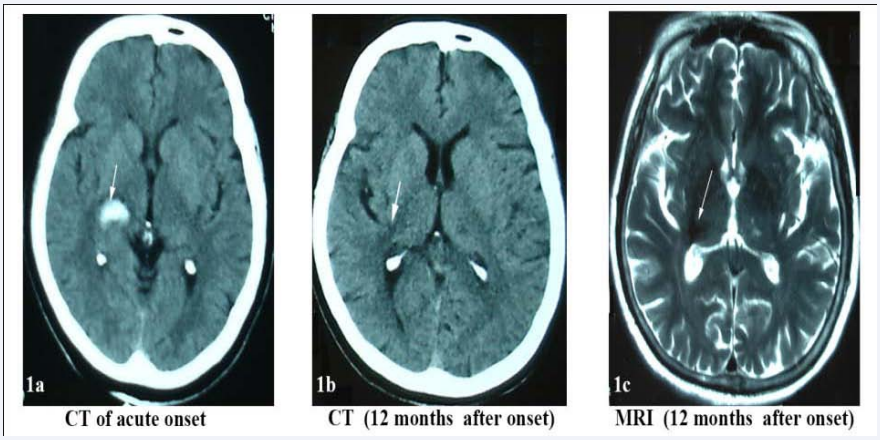

Figure 1 Skull image of case 1; 1a was CT scan on acute onset of thalamic hemorrhage; 1b was CT reexamination and 1c was T2WI /MRI of the patient at 1 year after the onset of ICH; The lesion was hypointense on T2WI.

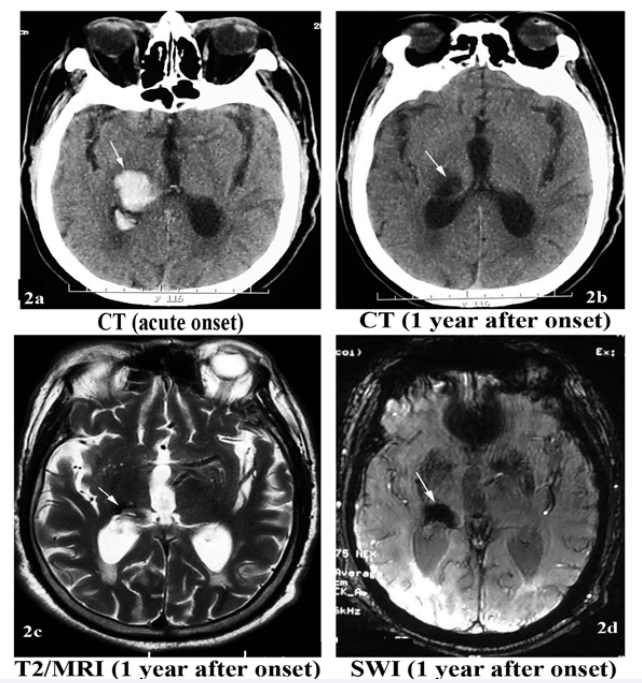

Figure 2 Skull image of case 2; 2a was CT scan on acute onset of thalamic hemorrhage; 2b was CT reexamination of the patient at 1 year after the onset of ICH, 2c and 2d were T2WI and SWI respectively of the case at 1 year after ICH; the lesion was hypointense on T2WI and SWI.

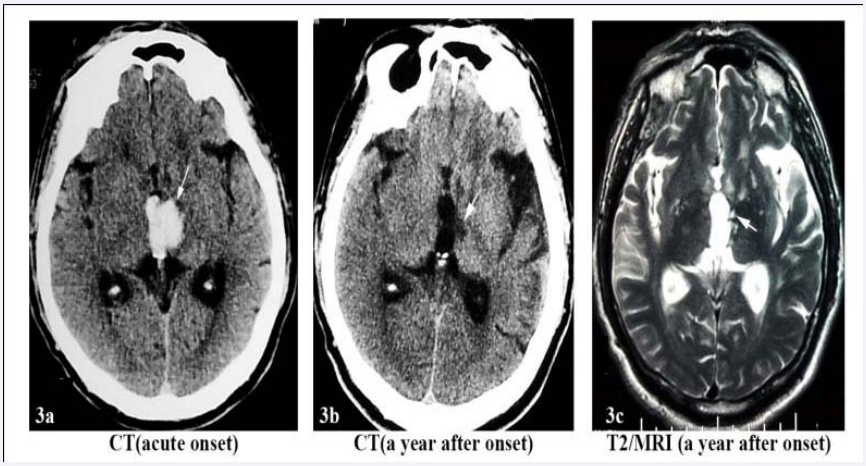

Figure 3 Skull image of case 3; 3a was CT scan on acute onset of thalamic hemorrhage; 3b was CT reexamination and 3c was T2WI /MRI of the patient at 1 year after the onset of ICH. The lesion was hyperintense on T2WI.

methemoglobin, short T1, long T2) and chronic (from 15 days on, hemosiderin rim) [6,12]. But there were few data to describe the character of MR over 6 months following ICH when the proteins had been swept away. Here we also provided Sequential images MRI from an ICH without CPSP. (Figure 3 brain MRI over 1 year following ICH). The former hematoma was seen as a long T2 signals at MRI.

As shown in Figure 1c and Figure 2c, over 1 year after ICH, the hematoma with CPSP was seen as a short signal on T2 weighted MRI. T2 shortening can also be produced with higher iron content (ferritin and hemosiderin) [2,5,6]. As shown in Figure 3C, the hematoma without CPSP was seen as a long signal on T2 weighted MRI. Haacke EM et al found that there is a negative correlation of iron with T2 hyperintensity. The higher the iron content, the less visible the lesions seem to be in T2-weighted images [7]. Moreover, there were a large low signal intensity around thalamic lesions on SWI phases in case 2 (as shown in Figure 2d). Because the SWI phase value is a linear function of iron concentration, the iron content can be quantitatively measured more easily than by using T2 methods [7]. SWI offers information about iron accumulations (such as deoxygenated blood, hemosiderin and ferritin) with low signal intensity.

Compared to ICH without CPSP, we have reason to believe iron

(ferritin or hemosiderin) may take part in the pathophysiology of central pain generation.

However, the observation of 2 CPSP patients coexisted with diabetes mellitus, the pathophysiology of the link between diabetes and CPSP has not yet seen in the literature; We still needs more information to confirm the relationship between the brain iron content and CPSP.

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