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REVIEW ARTICLE

Relationship between heterotopic ossification and traumatic brain injury Why severe traumatic brain injury increases the risk of heterotopic ossification

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Abstract Heterotopic ossification (HO) is a pathological phenomenon in which ectopic lamellar bone forms in soft tissues. HO involves many predisposing factors, including congenital and postnatal factors. Postnatal HO is usually induced by fracture, burn, neurological damage (brain injury and spinal cord injury) and joint replacement. Recent studies have found that patients who suffered from bone fracture combined with severe traumatic brain injury (S-TBI) are at a significantly increased risk for HO occurrence. Thus, considerable research focused on the influence of S-TBI on fracture healing and bone formation, as well as on the changes in various osteogenic factors with S-TBI occurrence. Brain damage promotes bone formation, but the exact mechanisms underlying bone formation and HO after S-TBI remain to be clarified. Hence, this article summarises the findings of previous studies on the relationship between S-TBI and HO and discusses the probable causes and mechanisms of HO caused by S-TBI.

The translational potential of this article: A better understanding of the probable causes of traumatic brain injury—induced HO can provide new perspectives and ideas in preventing HO and may support to design more targeted therapies to reduce HO or enhance the bone formation.

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Introduction

Heterotopic ossification (HO) is a pathological phenomenon that causes bone formation in nonosseous tissues, including muscles and connective tissues [1]. This disease is usually induced by fracture, burn, neurological damage (brain injury and spinal cord injury) and joint replacement [2]. Patients with HO experience swelling of tissues, inflammation, pain, limited motion and joint adhesion. All these symptoms significantly affect the lives and emotions of patients [3,4]. According to different inducements, HO can be divided into three types: myositis ossificans progressiva, traumatic HO and neurogenic HO [5]. By theory, HO may occur in any part of the body, but in most of the cases it occurs in the joints, such as in the hips, elbows, and shoulders. Depending on the inducements, the affected positions are different [4,6].

Roberts [7] first described HO in patients with brain injury and a prolonged period of coma. Researchers thereby found an internal relationship between HO and the nervous system. Recent studies have found that patients who suffered from bone fracture combined with severe traumatic brain injury (S-TBI) are at a significantly increased risk for HO [8]. The incidence of neurogenic heterotopic ossification (NHO) in patients with traumatic brain injury (TBI) is about 20%, but the rate of NHO exceeds 50% when TBI and femur fracture are concomitant [5]. In some cases, HO may be caused by brain or spinal injuries, without other injuries existing [9]. Studies determined the effect of TBI on fracture healing and confirmed that patients who suffered from both fracture and S-TBI are expected to show a faster rate of fracture healing accompanied by hypertrophic callus formation or heterotopic ossifications [10—12]. Fracture healing and HO share common initiating events (inflammation, angiogenesis, chondrogenesis and osteogenesis) [13]. Several researchers have speculated that the consolidated callus formation is a form of local heterotopic bone formation [14,15]. Spencer [16] conducted a histological analysis on the callus of a patient who suffered from fracture and S-TBI and found that the composition of callus is highly similar to that of the bone. Spencer also suggested that faster fracture healing and callus formation are indicative of HO [16].

Though TBI has been associated with faster fracture healing, enhanced callus formation and HO in both TBI patients and animal models, there are also evidences of enhanced bone loss and increased risk of fracture in brain injury patients [17,18]. Animal studies in rodents with TBI are consistent with the clinical studies [19—21]. However, it should be noticed that, most of the bone loss after TBI occurs in the absence of fracture. The increased callus formation in TBI combined with bone fracture occurs in the early stages postinjury while the bone loss symptoms appear in a latter period [22,23]. Faster bone fracture healing and HO are mostly linked to an S-TBI accompanied with breakdown of the blood—brain barrier, while the bone loss is usually investigated in a mild-TBI condition. Therefore, the condition and environment that enhanced bone loss or bone formation after TBI may have a great difference. Researchers have studied the association between TBI and HO for a long time, but the direct relationship between them remains unknown, and the pathological mechanism is yet to be elucidated. This article summarises the latest research findings and related perspectives about this issue, providing references for further understanding TBI-HO. Furthermore, the findings mentioned in this review may allow us to design more targeted therapies to reduce HO or enhance the bone formation.

Normally, Patients with brain injury are given corticosteroids, nonsteroidal antiinflammatory drugs, diphosphonates and radiotherapy as a preventative measure for HO [8]. Recently, several researchers proposed their hypotheses for the potential methods of HO prevention. Kan et al. [24] noticed that blocking of neuron-specific substance P (SP) signalling through the neurokinin 1 (NK1r) receptor can abrogate HO formation and suggested that inhibition of the SP receptor, NK1r, might therefore be a novel treatment for preventing the early events that lead to HO. Genêt et al. [25] found that ablation of phagocytic macrophages with clodronate-loaded liposomes reduced the size of NHO by 90%, supporting the conclusion that NHO is highly dependent on inflammation and phagocytic macrophages in soft tissues. All of these hypotheses or suggestions provide us with new perspectives and ideas for preventing HO.

Association between S-TBI and HO

Patients who suffered from fracture and TBI usually exhibit faster healing rate and increased callus formation [26]. Cadosch et al. [27] found that the time for bone union in patients with S-TBI was reduced by half when compared to patients with fracture alone. Callus formation in patients with S-TBI is 37—50% greater than that in patients with fracture alone. Consistently, studies in animal models combining TBI with bone fracture showed an increased volume of callus and a higher rate of gap bridging compared with the normal group or fracture group [22,28,29]. In addition, treating human osteoblasts with the serum of patients with S-TBI significantly promotes the proliferation of these cells. A number of studies also provided conclusive evidence for this view and found that serum after brain injury promotes the proliferation of osteoblasts and bone mesenchymal stem cells and the expression of intracellular alkaline phosphatase (ALP) [30—32].

In a subsequent study by Cadosch et al. [14], skeletal muscle cells were treated with the serum of patients with severe brain injury. The results showed that serum treatment significantly increases the level of intracellular ALP. A specific transcription factor of osteoblasts expresses and mineralises the formed nodule. These results indicate that the serum of S-TBI patients contains some humoural factors that promote the differentiation of osteogenitor cells in skeletal muscles into bone cells and mineralisation. In addition, blood—brain barrier permeability change, coma, mechanical ventilation, and inflammation caused by S-TBI are all important factors of HO induction. Table 1 summarises the relative factors in HO caused by S-TBI.

Effects of osteogenic factors released after TBI on fracture healing

Yang et al. [49] performed a comparative research on 74 patients who suffered from fracture alone or combined