Heterotopic Ossification of the Calvarium Following Bilateral Craniectomies in Traumatic Brain Injury

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Background: Heterotopic ossification (HO) is defined as ectopic bone formation following traumatic brain injury. Patients typically develop lesions in the hips, knees, and elbows that cause pain, restricted range of motion, nerve impingement, and pressure ulcers.

Case Report: We report an unusual presentation of HO in an 18-year-old male who was involved in a motor vehicle accident and subsequently developed malignant intracranial pressure. His HO developed following bilateral craniectomies in which 2 different dural substitutes were used. Radiographic timing of ectopic bone formation and its continued growth varied.

Conclusion: We describe a case of HO in the cranium, a condition that is underreported in the literature. Of significance, despite sustaining multiple traumatic fractures that were managed conservatively, our patient failed to demonstrate any evidence of ectopic axial HO following his incident.

Keywords: Brain injuries, decompressive craniectomy, dura mater, intracranial hypertension, ossification–heterotopic

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INTRODUCTION

Heterotopic ossification (HO) is ectopic bone formation in soft tissues of mesenchymal origin, ligaments, tendons, or muscles adjacent to joints. The development of bone in abnormal soft tissue results from an alteration in the normal regulation of skeletogenesis.[1] The formation of bone ranges from clinically insignificant radiographic findings to devastating clinical impairment. HO is associated with some rare genetic disorders; however, it more commonly has a multifactorial etiology. Risk factors include neurologic injury (both to the brain and spinal cord), major joint surgery (such as hip arthroplasty), burns, fractures, dislocations, and soft-tissue trauma.[1,2] Ectopic bone formation can cause significant pain, restricted range of motion, nerve impingement, and pressure ulcerations.[1,3] In the acute phase, HO presents with erythema, swelling, warmth, and rapid loss of joint motion; it can be painful during the process of formation; and it can occur 3-4 weeks following injury.[2] These formations can be detected radiographically as early as 4-6 weeks.[4] The incidence of HO following brain injury is infrequent; reported incidences vary from 11%-22%.[5,6] Patients typically develop lesions in the hips, knees, and elbows. We report the unusual finding of HO in the cranium following bilateral craniectomies in a patient who sustained severe traumatic brain injury (TBI).

CASE REPORT

An 18-year-old male with an unremarkable medical history was involved in a motor vehicle collision resulting in TBI. He also sustained humeral, pelvic, and tibia fractures. His initial Glasgow Coma Scale score was 7T; he was unable to open his eyes and was only localizing to painful stimuli. Head computed tomography (CT) imaging demonstrated right frontal contusions with evidence of diffuse axonal injury. An external ventricular drain (EVD) was placed with an opening pressure of 32 mmHg. The patient was originally managed medically for malignant intracranial pressure (ICP); however, on day 10, he became nonresponsive to these measures and subsequently underwent right decompressive craniectomy (Figure, A). Our scalp incision was taken down to the pericranium and reflected with the skin flap. The craniectomy was turned with the craniotome, leaving relatively smooth edges. Last, the dura mater was opened in stellate fashion, radially extended in several directions. DuraGen (Integra Life Sciences Corporation) was used as the dural substitute. Following surgery, ICPs continued to exceed 20 mmHg; therefore, the patient underwent a left decompressive craniectomy performed in similar fashion to the first craniectomy. Dura-Guard (Synovis Surgical Innovations) was used as the dural substitute for the second procedure. Postoperatively, the patient was placed in a pentobarbital coma, and his ICPs stabilized to <20 mmHg. Sedation and his EVD were weaned by day 31. Remarkably, the patient started following commands on day 34. He fully recovered from his brain injury, and 119 days after the initial insult he underwent bilateral cranioplasties. During the procedure, we discovered that thick pieces of bone had formed along the ridges on the right side (the
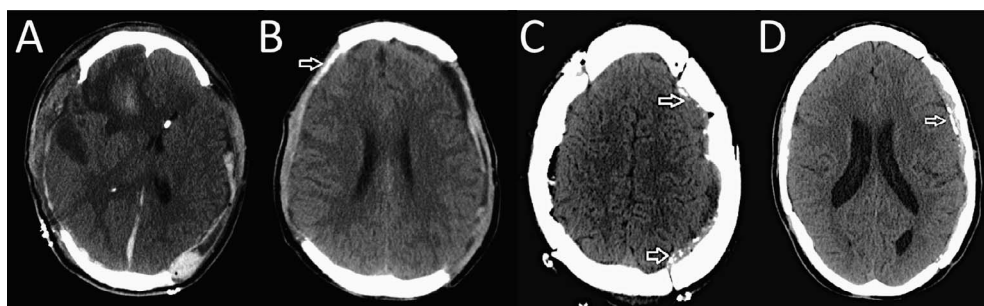
Figure. Axial noncontrast computed tomography imaging planes illustrate the progression of heterotopic ossification (HO). A. Image from postoperative day (POD) 1 after the bilateral decompressive craniectomies shows the DuraGen side on the right and the Dura-Guard side on the left. B. On POD 33, the patient had signs of early HO calcification on the right side that were not evident on the left. C. On POD 107, the right-sided calcification remained stable, but the calcification on the left side became evident. D. Calcification on the left side continued to expand on subsequent imaging on POD 160.

DuraGen side). On the left side (the Dura-Guard side), thin sheets of bone had formed along the dura itself, with an appearance similar to an eggshell. Pathology reported fragments of benign lamellar and woven bone (clinically HO). Reevaluation of the patient's imaging on day 33 after his bilateral craniectomies showed signs of early calcification on the right side that were not evident on the left (Figure, B). Following the patient's cranioplasties, the right-sided calcification remained stable, but the calcification on the left side (the Dura-Guard side) only became evident on the postoperative day 107 scan (Figure, C) and continued to calcify more as seen on subsequent imaging on postoperative day 160 (Figure, D). Of significance, the patient did not demonstrate any evidence of ectopic bone formation elsewhere despite his multiple traumatic fractures.

DISCUSSION

Ectopic bone formation in HO is believed to originate from mesenchymal stem cells that lie dormant in soft tissues and differentiate into osteogenic cells under appropriate stimuli. Three conditions are thought to be needed for HO to occur: a stimulating event, progenitor or mesenchymal stem cells, and an environment that allows osteogenesis.[7] The existence of an osteogenic precursor cell is self-evident. Although the nature of this cell is not established beyond the fact that it may arise from a mesenchymal stem cell, these cells are thought to play a pivotal role in the development of HO. However, failure of osteogenic induction is unlikely due to the lack of osteogenic precursor cells but rather is secondary to the presence or absence of an environment favorable for osteogenesis.

To date, the exact pathophysiologic mechanism for enhanced fracture healing and HO following TBI is not fully understood. Bidner et al suggested that osteoinductive factors are released by the injured brain into the blood circulation and act peripherally on the affected soft tissue.[8] In their series, serum samples from patients with isolated head injury as well as patients with head injury and lower extremity fractures demonstrated increased mitogenic activity, implicating a humoral mechanism in osteogenesis associated with head injury.

Little is currently known about the molecular pathways throughout which components of cerebrospinal fluid (CSF)

enhance osteoblastic activity. The osteoinductive potential of CSF was initially studied using in vivo rat models. The osteoinductive effect was explained as possibly attributable to the leakage of the CSF components into the blood circulation.[9] Gautschi et al analyzed CSF from 11 patients with TBI, 26 patients with nontraumatic brain pathology, and 46 control patients.[10] The study demonstrated a significantly higher proliferation rate in CSF analyzed from patients with TBIs than from control patients in a proliferation assay using fetal human osteoblast cell lines. Last, in a study that analyzed bovine CSF and bone morphogenetic protein levels, Dattatreyamurty et al found BMP-7 in CSF in concentrations sufficient to elicit a near-maximal biological response.[11]

An alternative theory to HO that may explain the findings in our patient may be from factors related to calvarial reossification. The ability for young children and immature animals to reossify calvarial defects is well described.[12,13] The dura mater, periosteum, and adjacent cranial edges have been implicated as regulators of osteogenesis in the calvarium.[14,15] Of these factors, the dura has been found to be the most potent.[16,17] Osteogenesis has been demonstrated when the dura was left intact, and lack of dural continuity causes an alteration in the integrity, ultimately resulting in a decreased rate of bone deposition following calvariectomy procedures.[13] The molecular mechanism for the increased osteoinductive capacity of the young, immature dura is not entirely known but is believed to be the result of increased expression of growth factors (transforming growth factor beta) and extracellular matrix molecules (collagen type II and alkaline phosphatase).[17] However, this osteoinductive capacity is generally lost in children >2 years of age.[18] Based on our operative approach—creating a stellate durotomy without preservation of the pericranium and using an onlay dural substitute—calvarial osteogenesis is less likely the etiology in our 18-year-old patient with TBI.

CONCLUSION

This case provides a unique insight into the pathophysiology of HO, with the rare finding within the cranium and the variation in its formation given the different dural substitutes used for our patient. It is unclear at this time how DuraGen and Dura-Guard play a role in the molecular environment and affect osteoinductive factors; however, a difference can

be appreciated in our case. Further research is necessary to determine the exact mechanism and optimal management strategy in this population.

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