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Review Article

Hylonome

Heterotopic ossification following traumatic brain injury and spinal cord injury: insight into the etiology and pathophysiology

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Abstract

Neurogenic heterotopic ossification (HO) is the ectopic formation of lamellar bone in non-osseous tissues following traumatic brain or spinal cord injury. The associated complications affect greatly their quality of life. This fact has shifted the focus of scientific effort towards the investigation and understanding of related risk factors and the pathophysiological mechanisms. Recent advancements include the investigation for genetic predisposition and association various biomarkers. In the present article we will analyze the current concepts on this topic, based on clinical and physiological evidence and we will discuss the potential areas for future research on this field.

Keywords: Heterotopic, Ossification, Trauma, Brain Injury, TBI

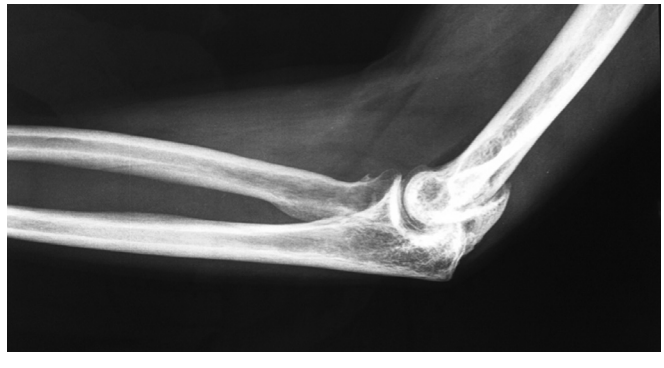
Introduction

HO is defined as the formation of mature, lamellar bone in non-osseous tissue, usually between the muscle and the joint capsule. Histologically and radiographically, heterotopic bone resembles normal mature bone but it can be easily distinguished from simple calcifications by the nature of its osteoblastic capacity[1,2]. Although there are rare hereditary disorders associated with HO, it is well established that HO is usually acquired following soft-tissue trauma, fractures (commonly in acetabular and elbow fractures followed by internal fixations), dislocations, elective orthopedic surgeries (e.g. hip surgery), electrocution and burn injuries and neurological damage.

Specifically, for neurogenic HO following TBI and SCI (Figures 1 & 2), the incidence of ectopic bone formation has been reported to be between 10% and 23%[3-5] and 40-50%[6-8] respectively. Other neurologic conditions associated with neurogenic HO such as Guillain-Barré syndrome (GBS), tumors and infections of the Central Nervous System (CNS), although reported, are not well documented and related data are scarce.

To date, multiple studies strongly suggest that the bone remodeling pathways leading to HO are more complex than previously thought, however the exact pathophysiological mechanism is not fully understood. It has been suggested that there are pathways of the immune system, the central nervous system and the indigenous inflammatory response that lead to

Figure 1. Lateral radiograph of the right elbow showing the ectopic bone formation over the olecranon fossa at the posterior and distal aspect of the humerus in a 32-year-old male with a recent traumatic brain injury.



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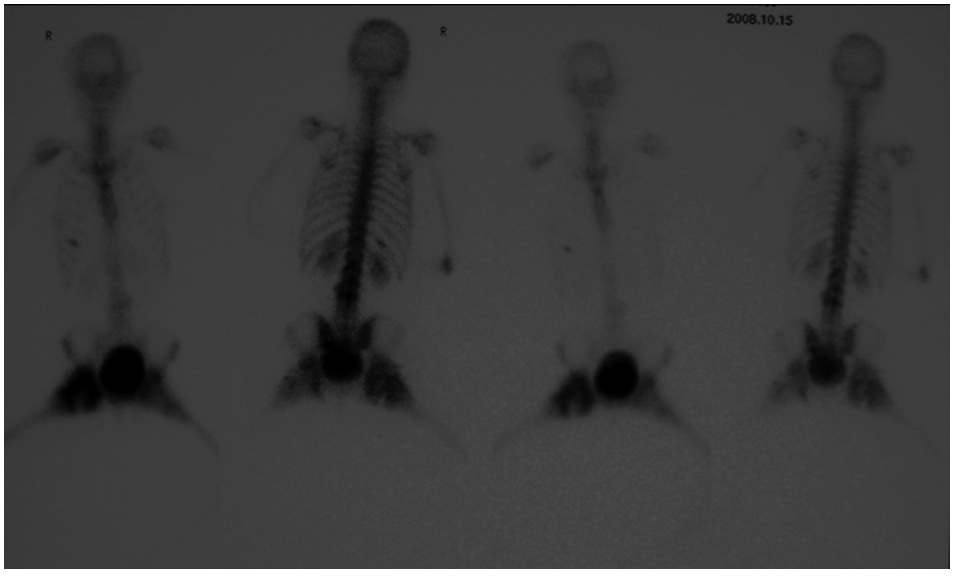

Figure 2. Three-phase bone scan of a 39-year-old with a history of a traumatic brain injury due to a motor vehicle accident showing increased concentration of Tc-99m-MDP at both hips, mainly the right one, which is consistent with active "immature" heterotopic bone formation.

the release of osteoinductive factors resulting in HO′. As, firstly, suggested by Chalmers et al.[9], HO is the result of the interaction of 3 conditions, which should necessarily be met. The presence of (a) an osteoinductive factor, (b) osteoprogenitor cells, and (c) an environment which is permissive to osteogenesis. This has been furthered investigated and nowadays is commonly accepted that HO requires stimulation of mesenchymal cell recruitment, proliferation and differentiation, followed by osteoprogenitor maturation and osteoblast activation[10]. Several groups of investigators have established a clear connection between the humoral factors released by the injured CNS and the following events (i.e. oxidative stress, effects of mechanical ventilation, free radical formation etc) leading to the development of neurogenic HO[11-16].

Trauma or Surgery	Neurological damage
History of previous HO	Genetic Predisposition
Pressure ulcers	Burn injuries and Electrocution
Paget's Disease	Ankylosing Spondylitis
Heterotrophic Osteoarthrosis	Diffuse Idiopathic Skeletal Hyperostosis
Rheumatoid Arthritis	Post-traumatic Arthritis
Osteonecrosis	Osteoarthritis
Hip dysplasia	Urinary tract infections
Nephrolithiasis	Deep Vein Thrombosis
Hemophilia	Sickle Cell Anemia
Tetanus	Amputation

HO, Heterotopic Ossification

Table 1. Cumulative Table of Risk Factors for HO[17-21].

Etiology and risk factors of NHO

Although there are a few risk factors especially investigated only for neurogenic HO, which they will be discussed at the end of this chapter, the general risk factors of HO still apply to neurogenic HO and must be mentioned here.

The generally established risk factors for HO are shown in Table 1.

Of these factors only a few have been investigated in patients with TBI and SCI with the last four presenting a special interest for neurological patients:

- Demographic factors (Sex, Age, Race): Male sex[17,18] and young age (20-30 years old)[19] have been suggested to be a risk factor for neurogenic HO formation but it has not been established yet. Race, however, it is not significantly correlated with the development of neurogenic HO[20,21].
- Genetics: As previously mentioned, the fact that not all patients with similar patterns and demographics develop neurogenic HO, has evoked the theory that certain individuals are genetically predisposed to neurogenic HO and generally HO formation, which maybe triggered by environmental influences.

i. HLA-Type Antigens

First, in 1981 Larson et al.[22] in a study of 43 patients with SCI, found that not only the HLA-B27 antigen was expressed in 5 of the 21 patients with HO, but also that none of the 22 patients without HO expressed it.

In the following years, the literature data are more differing yielding some or no association with HLA type antigens. Although some other HLA antigens have been suggested (HLA-

B18, HLA-B27 and DW7), subsequent publications associated only HLA-B18 with NHO. However, it is still observed that up to 75% of patients with neurologic injury that develop HO are HLA-B18 negative[6,22-25].

ii. Hereditary Disorders

It is a fact that a genetic predisposition of neurogenic HO has not yet directly been established and for this reason the research community has shifted interest into genetic disorders that may shed light into the genetic causes of neurogenic HO.

Fibrodysplasia ossificans progressiva (FOP) is an autosomal dominant disorder leading to ossification in the same locations as does HO secondary to TBI and SCI, with congenital malformation of the big toes, with valgus hallux deformities and tumor like swelling on the head, neck, shoulders and back. In FOP has been observed an overexpression of bone morphogenetic proteins (BMP-4)[26] and an under-expression of its antagonists (noggin, gremlin, follistatin and chordin)[27,28] resulting to a subsequent increased differentiation of osteogenic cells.

Later, Shore et al.[29] identified a specific mutation that existed in all known cases (hereditary and sporadic) of FOP. In other words, he found a highly specific codon for the particular disease, which can lead to new insights into the treatment of HO[26].

Progressive osseous heteroplasia is also another autosomal dominant disorder under research for its association with the genetic predisposition of HO but no significant result is published up to date.

Finally, the possible genetic predisposition of HO, and consequently neurogenic HO, is also supported from the fact that patients with ankylosing spondylitis, heterotrophic osteoarthrosis and diffuse idiopathic skeletal hyperostosis have a higher risk of HO[30,31].

a. Single Nucleotide Polymorphisms (SNPs)

As stated before, although it is extremely unlikely that a single "HO gene" exists, the investigation of the genetic predisposition of HO formation will help us immensely not only in the treatment but also, and more importantly, in the prophylaxis oh HO by helping us identify the "at-risk" patient earlier.

Mitchell et al.[16] in a recent study investigated and presented three possible genetic associations with the development of HO. Three single nucleotide polymorphisms (SNPs) from the adrenergic, the immune and the alternative complement systems each, showing a clear representation of the interplay of multiple pathways that affect bone remodeling. However, we must underline that, although 61 SNPs from six different metabolic systems were investigated, only those 3 systems yielded significant results. The less common polymorphism of the β2-adrenergic receptor (ADRB2) gene was associated with increased risk of HO and the toll-like receptor 4 (TLR4) and the complement factor H (CFH) were associated with a decreased risk of HO formation. Interestingly enough there has already been an association between bone remodeling and those three metabolic systems (inflammatory, immune and the central and sympathetic nervous system)[32,33].

iii. Trauma

Trauma as a risk factor of HO, and neurogenic HO in the case of TBI and SCI, is one of the most investigated factor associated with HO formation. There is a wide range of situations from a direct injury (e.g. combat-related trauma) to the result of a aggressive passive joint manipulation as trigger of heterotopic bone formation. Especially for neurologically impaired patients, several studies have suggested an increased incidence of HO after TBI and SCI with an associated trauma.

Finally, the association of trauma to HO formation has also been tested in rabbit studies[36-38] where the forcible passive movement of previously immobilized legs resulted in ectopic bone formation. Adapting the previous scenario in clinical medicine, this issue is present in critical ill patients in the Intensive Care Unit setting with burns, multiple injuries and paraplegia, which are also "high-risk" groups for HO formation. However, Casavant et al.[39] and Linan et al.[53] concluded that passive range of motion (PROM) and early mobilization of patients with TBI and HO is safe, which is nowadays the consensus of the clinical world in terms of not only treatment but also prevention of HO[6].

iv. Coma

Prolonged coma has been associated with the development of neurogenic HO, but no further investigation has been done on this subject[19].

v. Completeness and level of SCI

Completeness of the spinal cord lesion is more predictive than the level of the injury.[19]

1. Artificial Ventilation

Studies[35,40] have proposed that artificial ventilation may be a risk factor for neurogenic HO formation. A decrease in oxygen supply has been shown to affect osteogenesis: bone cell proliferation is increased by low oxygen concentrations and macromolecular synthesis is favored by high oxygen concentrations[40]. The proposed mechanism behind the association of artificial ventilation and HO formation is that an increased duration of artificial ventilation (extremely common in patients with TBI and SCI) may alter the homeostasis of the patient, especially in terms of electrolytes (calcium and phosphorus) and acid-base balance (oxygen tension and pH changes). However, no study has yet to establish a clear connection between those two, or even investigate the differences in local oxygen tension, local pH differences and local electrolyte disturbances at the site of HO.

Finally, another theory of the association of artificial ventilation and HO formation suggests that the attempted iatrogenic hyperventilation on the acute phase of traumatic brain injured patients, in order to lower intracranial pressure by reducing pCO2, may result in systemic alterations. The blood pH becomes more alkaline resulting in increased risk of salt precipitation, specifically of calcium precipitation[41], which may promote a more rapid formation of callus and accelerated fracture healing[42].

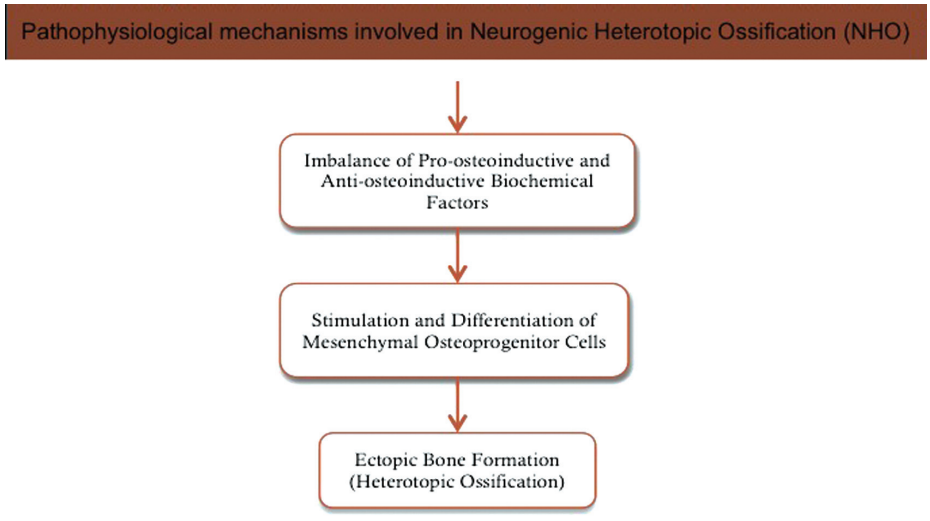

Figure 3. Pathophysiological mechanisms involved in Neurogenic Heterotopic Ossification (NHO).

2. Plegia and muscular spasticity or hypertonia

Marked muscle spasticity or hypertonia is extremely common symptom of CNS injured patients and has been suggested as a risk factor in numerous studies[6,43-46] as a cause of muscle hypoxia and increased risk of muscle tears from active or passive mobilization.

Pathophysiology of neurogenic HO

The exact pathophysiology of neurogenic HO is not clear yet. Initially, HO presents histologically as local microvascular alterations, vascular stasis with circumscribed edema and swelling. Following, it is observed a fibroblast and osteoblast proliferation, osteoid formation and finally ectopic bone deposition[45]. Several studies, with most representative that of Bidner et al.[7] and Kurer et al.[14], provided a clear evidence for the hypothesis of a humoral mechanism for accelerated fracture healing with increased bone formation after TBI and SCI. Gautschi et al.[15] even suggested an osteoinductive effect of the cerebrospinal fluid (CSF) from patients with severe TBI. Most recent studies[13,47] support this by examining the proliferation rates of hFOB cells or primary human osteoblasts.

As a result of the aforementioned specifics-facts in combination with the clinical presentation of neurogenic HO and the theory of Chalmens[9], the postulate theory for neurogenic HO formation is that it occurs from the induction of muscle progenitor cells from the mitogenic and osteogenic effects of the serum of CNS injured patients. In detail, the induction is believed to be the result of an imbalance of local and/or systemic factors in soft tissue following traumatic injury (Figure 3). In other words, it is believed that it is not so much the pro-inflammatory and osteoinductive biochemical factors that give rise to neurogenic HO, but the balance-ratio of pro-osteoinductive and anti-osteoinductive mediators located on the soft tissues. Furthermore, the current trending theory of neurogenic HO formation also supports the interactions of "signaling molecules" secreted from the injured tissue (such as the spinal cord) with not only local but also circulating progenitor cells in the immediate period after trauma. As a consequence we have the aberrant commitment, growth and differentiation of these cells into osteoblasts and finally ectopic bone formation[48]. This is substantiated by the fact that muscle-derived mesenchymal stem cells (MSCs) have been shown to be inherently plastic, enabling them to differentiate along multiple lineages (osteo-, chondro- and fibroblast, adipocytes, smooth muscle cells and also have the ability of stimulation, proliferation and differentiation of resident progenitor cells). However, very little is known to the involvement of MPC differentiation and the signaling pathways between them and the osteoinductive-released biochemical factors. Many humoral factors have been tested in numerous studies (e.g. alkaline phosphatase (ALP), creatine kinase (CK), prostaglandins (PGs)) but there is no conclusive evidence of a direct association between any of them and neurogenic HO formation.

Hereby, we will provide a concise review of the consensus of recent studies on the nature of those humoral factors and the suggested mechanisms involved based on Chalmers[9] prevalent theory:

1. Presence of Osteoprogenitor Cells

There is strong evidence of the presence of these potential osteogenic cells in most adult connective tissues (e.g. muscle and fascia) and organs[9,49]. In more detail it is observed that the mineralized nodules, which later lead to bone formation, arise from vimentin-positive spindle-shaped cells[47]. Some of these spindle-shaped cells, present in skeletal muscle, have been associated to mesenchymal stem cells, bone-marrow stromal cells and pericytes because of their similar morphological, im-

munohistochemical and mRNA profiles and their capacity for multilineage differentiation as mentioned before[47,49-51].

Concluding, the well-established presence of mesenchymal stem cells within muscle tissue is believed to be the site of action of the osteoinductive factors released in the systemic circulation by the injured CNS.

2. Osteoinductive Factors

a) Autonomic Dysregulation

Major et al.[52] concluded that local microvascular alterations, edema and prolonged swelling (similar histological characteristics as the initial phase of heterotopic bone formation) can appear in the involved tissues as a result of sympathetic activity. Campos da Paz et al.[43] speculated that an interruption in neural pathways, from a TBI or a SCI, would result in a chaotic regulation of bone growth. Specifically it was hypothesized that a dysfunction of proprioception, from the CNS injury, would make the ligaments to react to stimulus (e.g. forceful manipulation from intensive physical therapy) in an independent, isolated way resulting to a chaotic differentiation of mesenchymal osteoprogenitor cells into heterotopic bone. Contrary to this, the consensus of the rehabilitation world and of recent studies is that active or passive exercising of joint within the pain-free range has a favorable effect in the maintenance of a good physical condition, diminishing the need for additional treatment[6,53].

Relevant to the nervous dysregulation secondary to CNS trauma, are the previously established role of the hypopituitary humoral axis after head trauma[2,54,55] and the production of growth factors from the brain and pituitary glands[5,56]. It has been suggested that those sites secrete systemic growth factors that may lead to heterotopic bone formation, however, it is also suggested that the activity of those systemic growth factors can be blocked by being bound to plasma proteins[57,58].

b) Altered immunity and abnormal inflammatory response to neurological damage

The examination of the serum from TBI patients has shown an increase in various humoral factors especially of inflammatory nature. There is a consensus among researchers that the serum from CNS injured patients, even in the very first hours post-trauma, shows increased levels of several biochemical markers, including C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), Interleukin-6 (IL-6), Parathyroid Hormone (PTH), Alkaline Phosphatase (ALP), some of which we will discuss in more detail. However, we must underline that those laboratory findings, although useful, have a disputable specifity especially in critically ill patients with concurrent infections, tracheostomies and recent surgeries. The following biomarkers have been suggested in relation to neurogenic HO formation:

- Inflammatory markers:

Serum CRP has been shown to increase in patients with a severe TBI when compared to patients without TBI[13,59], indicating a strong acute-phase inflammatory response.

Although high levels of interleukin-6 (IL-6) characterize the inflammatory phase of bone healing[60] and IL-6 has been established as a powerful predictor of early neurological deterioration[61], there is no direct association of their effect on NHO formation.

Also, tumor necrosis factor-alpha (TNF-a), another cytokine of inflammatory nature, due to its dependence to interleukins, is being investigated as a potential biomarker of HO formation. Especially interesting is the fact that TNF-a is released from astrocytes and microglia achieving high concentrations soon after TBI[62,63].

Leptin has been shown to promote local activation of bone progenitor cells and osteoblasts but also to decrease osteoblastic activity by binding to hypothalamic neurons. Serum leptin levels were found low in patients with neurogenic HO[64,65] but no casual relation was established between the low leptin levels and neurogenic HO. Furthermore, the fact that no differences were found across the groups of the studies in terms of renal function, food intake or body fat arose the question of possible connection between leptin levels and hypothalamic damage contributing to neurogenic HO formation.

- Osteoblastic markers:

PTH was also significantly increased in TBI patients as early as 6-hours post trauma according to Gautschi et al.[13] and Trentz et al.[66]. PTH as a regulator of homeostasis of calcium and phosphate is considered to play a significant role in the enhanced bone formation observed in TBI patients. Contrary, a recent study[47] showed no significant differences in serum PTH between the different groups of the study at any tested time post-trauma.

For ALP the data are disputable since in recent studies, despite the observed increase throughout the examined period post-trauma, there has not been shown any statistically significant different ALP levels between patients with head trauma and patients without head trauma (fracture group or control group)[35,47].

Respectively for serum calcium, the data are also controversial with studies showing no significant change between all groups[35,66] and studies showing significantly lower serum calcium levels in patients with a TBI than in the other groups[47].

Another protein associated with neurogenic HO is osteocalcin. It is an important marker for bone remodeling[67]. In experimental level[68,69] has been suggested to induce matrix secretion and recruitment of bone-resorbing cells. Trentz et al.[66] found osteocalcin to be significantly lower in patients with combined or isolated TBI, suggesting the possible predictive role of osteocalcin levels in future ectopic bone formation.

Finally, an increased expression of marker genes of osteoblastic differentiation RUNX-2, SP-7 and CATK has been observed in the serum of TBI patients[13]. RUNX-2 and SP-7 are transcription factors for osteoblastic differentiation and CATK is a marker of osteoblastic activity[13].

- Bone turnover markers:

Trentz et al.[66] in a study of 80 patients with TBI supported the previously expressed theory of imbalance between pro-osteoinductive and anti-osteoinductive factors in the TBI patients by investigating Carboxyl-Terminal Propeptide of Type 1 Pro-

collagen (PICP) and Carboxyl-Terminal Pyridinoline Cross-Linked Telopeptide of Type 1 Collagen (ICTP) levels. Specifically, not only PICP levels were above the normal range and higher than in other groups in patients with TBI (showing an enhanced osteoblastic activity[70,71]) but also ICTP levels were lower in patients with isolated or combined TBI (showing a decreased osteoclastic activity[72,73]).

From the two IGFs, IGF-II has been suggested to play a role in HO formation as it is known to stimulate type 1 collagen production and cartilage matrix synthesis but the data are inconclusive.

- Osteogenic differentiation and other markers:

Bone morphogenic proteins (BMPs), which belong to the TGFbeta superfamily, specifically BMP-9 and BMP-2, have been investigated on recent studies for their osteoinductive influence and involvement in HO pathophysiology. They are known to induce not only mesenchymal and osteoprogenitor cells, but also osteoinducing factors such as insulin-like growth factor (IGF) and vascular endothelial growth factor (VEGF) leading to the regulation of osteoblast differentiation and bone formation[74,75]. However, a recent study of Gautchi et al. concluded that BMPs in CSF from TBI patients are not present in high enough concentrations to be responsible for the osteogenic cell response that triggers HO[15].

Basic fibroblast growth factors (FGFs), another member of the TGFbeta superfamily, known to undergo a rise after a fracture as they stimulate fibroblast activity[76], were shown to increase up to seven times than normal in head injured patients with a concurrent local injury[77].

Matrix Metalloproteinases (MMPs), involved in numerous remodeling processes, including bone remodeling phase and angiogenesis through their degrading capabilities, are involved in NHO research because of their potential of biomarkers of brain tissue damage and, consequently, neurological outcome[78]. Specifically, MMP-9 is found in high levels in acute TBI patients, and in correlation with high levels of IL-6 after TBI, it is believed to play a crucial role n the post-TBI inflammatory events[79].

The WNT signaling pathway is a class of signaling factors (proteins) required for the development of several types of tissues including musculoskeletal. There has been an increased interest for the WNT genes because it has recently been shown that mutations of those pathways result in disorders of deficient or excess bone formation[80]. In the future we hope to manipulate pharmacologically those pathways, for orthopedic applications including HO.

Lastly, 24-hour urinary hydroxyproline has also been observed in spinal cord-injured patients with HO formation but there has not been further investigation of its clinical diagnostic importance[81].

We should also mention various factors that have been investigated in a more experimental level, with scarce though research data. Lately there has been an increased interest of the research community towards prostaglandins (PGs). It is being investigated not only their role as biochemical inflammatory factors on heterotopic bone formation[38] but also how their inducing factors (e.g. BMP-2 and PTH) result in different actions of PGs on bone homeostasis[82]. However the research of these factors is still evolving with no direct clinical correlation yet.

3. Permissive Environment

Despite the aforementioned osteoinductive capacity of the humoral factors secreted systemically by the injured tissue and acting locally on the site of HO formation, it is also investigated the osteoinductive capacity of the local changes occurring right after soft tissue trauma. The hypothesis is that there is interplay between the release of local osteoinductive factors and the local environmental changes.

Locally observed contributing factors include salt precipitation and electrolyte disturbances, tissue hypoxia, pH changes, changes in local sympathetic nerve activity, immobilization or forcible mobilization after prolonged immobilization, local disequilibrium between parathyroid hormone and calcitonin[83]. It is known[84] that even in the normal process of fracture healing there are occurring changes in local blood flow, associated with pH changes and changes in serum calcium levels, but also significant alteration of local pO_2 in the fracture callus[40,85].

However, many clinical studies[86-88] have described HO in critically ill internal medicine patients and in patients with complicated organ transplantation, meaning in patients without local injury on the site of developing HO. This contrasts the importance of a permissive local environment but supports the theory of systemic factors inducing HO. Nonetheless, it is also conceivable that localized pressure caused by supine positioning of these patients may play a role but it is not investigated yet.

Management and Prognosis

1. Pharmacological Interventions

The role of indomethacin and other NSAIDs in prevention of HO is extensively reported[89,90]. They have been shown to inhibit cyclo-oxygenase, which is needed for the production of prostaglandin E2 that is thought to be a mediator in heterotopic bone formation. Banovac et al.[89] highlighted the prophylactic effect of indomethacin or rofecoxib compared placebo treatment in patients with spinal cord injuries. They found a significantly lower incidence of HO in the treatment group (25.0%) compared to the placebo group (64.7%) ($p<0.001$). Additionaly, HO symptoms presented significantly later than those in the placebo group (31.7 days vs. 19.2 days; $p<0.048$).

The use of bisphosphonates, and specifically etidronate, in patients with HO due to TBI patients is generally limited[91]. The theoretical effect thereof ois associated with a potential delay in mineralization of the osteoid. Etidronate that is administered prophylactically within a week of injury for 6 months was associated with decreased radiographically and clinically evidenced development of HO when compared to those without treatment ($p<0.025$). Study results indicate that there is Level 2 evidence that etridonate reduces the development of heterotopic ossification in severe head injury patients. In a prospective controlled trial Banovac et al.[92]

Author	% HO with isolated TBI/SCI	% HO with concurrent local injuries (fractures, dislocations)
Garland and O'Hollaren ([34] 1982)	4.0 %	89.0 %
H.C. Pape et al. ([35] 2000)	3.3 %	93.3 %
Gautschi et al. ([13] 2009)	N/A	41.67 %

HO, Heterotopic Ossification;TBI, Traumatic Brain Injury; SCI, Spinal Cord Injury; N/A, not applicable.

Table 2. Papers reporting on the incidence of HO when there is an isolated TBI/SCI versus the incidence of HO with concurrent local injuries[13,34,35].

Traumatic Brain Injury (TBI)	Spinal Cord Injury (SCI)
Genetic Predisposition (e.g. HLA-type antigens, SNPs)	Guillain-Barre Syndrome (GBS)
Tumors of CNS	Infection of CNS (e.g. Encephalitis)
Vascular Disorders (e.g. Stroke, Subarachnoid Hemorrhage)	Marked muscle Spasticity or Hypertonia
Epidural Abscesses	Prolonged Coma
Completeness and Level of SCI	Artificial Ventilation

NHO, Neurogenic Heterotopic Ossification.

Table 3. Cumulative Table of Suggested Risk Factors of NHO.

compared the intravenous etidronate (given for 3-5 days) followed by oral etidronate treatment for 6 months with the oral-only editronate treatment for 6 months. The authors showed that there is no significant difference between the two groups in the development of HO. However, intravenous etidronate treatment significantly reduced swelling from baseline ($p<0.01$). In another study, Banovac et al.[93] reported that treatment with intravenous etidronate treatment followed by oral etidronate treatment for 6 months can halt post-SCI HO progression if initiated before radiographic evidence is present. However, there is no substantial evidence of improvement in SCI patients with clinical signs of HO following long term (2 years) etidronate treatment. Garland et al.[94]. Overall, results of these studies indicate there is Level 4 evidence that etidronate is not effective in treating HO post SCI once there is radiographic or clinical evidence of HO. Recent experimental data indicate that nuclear retinoic acid receptor-γ agonists are potent inhibitors of heterotopic ossification in mouse models and, thus, may also be effective against injury-induced and congenital heterotopic ossification in humans.

2. Non-Pharmacological Interventions

Several non-pharmacological interventions, including both operative and non-operative treatment modalities, have been tested for the prevention and/or treatment of HO after traumatic brain injury during the recent years. There is Level 4 evidence that surgical excision alone does not significantly improve HO post SCI[95]. This specific study found profound functional improvement directly following surgical excision that did not remain throughout a mean period of 6 years. Specifically, 12.5% of the individuals returned to preoperative levels or worse and total recurrence rate for HO in the hip joint was 92%.

The use of radiotherapy post-surgical excision of HO was studied in two case series in patients with SCI[96,97]. The studies indicated that progression or recurrence of the excised bone is prevented in 71%[96] and 90.9%[97] of the cases. Furthermore, combined surgical treatment and irradiation is associated with significant improvement in ROM for 82% of patients, 64% of whom maintain their ROM or gain further range through rehabilitation.

Prophylactic pulse low intensity electromagnetic field therapy with range of motion and exercise therapy has been found to be effective in progression of the disease[94].

3. Multi-modal approach

The use of pharmacological treatment in combination with surgical excision, irradiation, physiotherapy has been introduced as a superior holistic approach of patients with HO post traumatic brain injury during the latest decade. Fuller et al.[98] reported on a case series of 17 brain injury patients who underwent surgical excision of knee HO followed by etidronate treatment. A significant increase in range of motion (average 65°) was documented without clinical or radiographic recurrence of HO. Moore[99] presented similar results in 17 cases after surgical excision of HO at hips and elbows due to traumatic brain injury that was combined with etidronate treatment for the prevention of secondary HO. Twenty-three months post-surgery, the immediate postoperative range of motion was maintained after an average 23 months period. De Palma et al.[100] found that the benefit of multimodal approach in range of motion is greatest in patients with the largest restriction preoperatively.

The importance of continuous passive motion (CPM) in addition to surgical excision and indomethacin administration was highlighted by Lazarus et al.[101], who presented a series of 24 patients with traumatic brain injury and elbow HO. The maximum flexion and extension increased significantly at 2 years postoperatively ($p=0.0003$, 0.0005 respectively) with the patients that received CPM demonstrating higher gain in range of motion than those that did not receive CPM ($p=0.04$)

Conclusion

In conclusion, neurogenic heterotopic ossification is a complex and common clinical oddity that provokes difficult prob-

lems to patients and physicians. The research community has already identified numerous clinical factors and biochemical markers that are predictive of eventual neurogenic HO and has explained various pathways involved in the pathophysiology of neurogenic HO. However, to date, the entity of neurogenic HO is not clear leading to diagnostic and, mainly, therapeutic anomalies. We believe that future research should investigate in more detail the genetic and bio-molecular element of neurogenic HO, as still, very little is known on this level. Finally, it is crucial to emphasize that a better understanding of neurogenic HO will not only help us immensely in the prophylaxis and treatment of Heterotopic Ossification but will also broaden our knowledge in other common orthopedic problems such as fracture non-union.

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