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Neurological heterotopic ossification: Current understanding and future directions

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ABSTRACT

Neurological heterotopic ossification (NHO) involves the formation of bone in soft tissue following a neurological condition, of which the most common are brain and spinal cord injuries. NHO often forms around the hip, knee and shoulder joints, causing severe pain and joint deformation which is associated with significant morbidity and reduced quality of life. The cellular and molecular events that initiate NHO have been the focus of an increasing number of human and animal studies over the past decade, with this work largely driven by the need to unearth potential therapeutic interventions to prevent the formation of NHO. This review provides an overview of the present understanding of NHO pathogenesis and pathobiology, current treatments, novel therapeutic targets, potential biomarkers and future directions.

1. Introduction

Heterotopic ossification (HO) is characterised by the formation of bone in soft tissue. HO frequently occurs due to neurological insult (i.e., NHO), of which the most common are traumatic brain injury (TBI) and spinal cord injury (SCI) [1–3]. Development of NHO is often initiated following polytrauma involving concomitant central and peripheral injuries, however, HO also follows a number of non-neurological conditions, including hip replacement surgery [4], bone trauma [5], and burns [6], and can be associated with some rare genetic diseases (i.e., fibrodysplasia ossificans progressiva; FOP and progressiva osseous hyperplasia) [7,8]. NHO often forms around the hip, knee and shoulder joints, causing severe pain and joint deformation that can progress to complete joint fusion [9–11]. Surgical excision is currently the only treatment option for mature HO/NHO, however ectopic bone formation commonly recurs following surgical intervention [12,13]. Until recently the mechanisms through which trauma to the central nervous system (CNS) facilitates ectopic bone formation were largely understudied and poorly understood, and as such pharmaceutical interventions to prevent the development of NHO have shown limited efficacy [14,15]. Therefore, the cellular and molecular events which may trigger NHO have been the focus of an increasing number of pre-clinical and clinical studies over the past decade, with this work largely driven by the urgent need to develop prophylaxis. This review provides an overview of the current understanding of NHO pathogenesis and pathobiology, current treatments, possible therapeutic targets, potential biomarkers, and future directions. Because there are a limited number of studies specifically examining NHO, and the various forms of HO likely share some common pathological mechanisms, where appropriate we will discuss findings from studies featuring HO that may bare relevance to NHO.

2. The clinical problem of NHO

Recent studies generally suggest that NHO effects 20–29% of SCI patients, and 5–20% of severe TBI patients (i.e., Glasgow Coma Scale ≤8) [3,16–21]. NHO requiring surgery, however, is more common following TBI than SCI [3,16,17,22,23]. Some reports suggest that the prevalence of NHO is higher in men, which may be due to the increased number of men who experience a TBI or SCI, while other studies suggest that the prevalence of NHO does not differ between sexes [18,24,25]. It should be noted that the prevalence of NHO reported in the literature is varied, which, may be due to the lack of consensus on the definition and classification of NHO. NHO is commonly defined as the formation of bone in soft tissue associated with neurological trauma [16], however the severity of TBI or SCI that is required to differentiate HO from NHO has not been defined and often the injury severity is not well reported.

Abbreviations: ACVR1, Activin A receptor, type I; BMP, Bone morphogenetic protein; bTBI, Blast-related traumatic brain injury; CNS, Central nervous system; FOP, Fibrodysplasia ossificans progressive; HIF-1α, Hypoxia inducible factor alpha; HO, Heterotopic ossification; NHO, Neurological heterotopic ossification; NKr, Neurokinin receptor; OSM, Oncostatin M; RAR, Retinoic acid receptor; SCI, Spinal cord injury; SP, Substance P; TBI, Traumatic brain injury; TRPV1, Transient receptor potential vanilloid subfamily, member 1; VEGFα, Vascular endothelial growth factor alpha.

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The prevalence of NHO reported may also vary due to several factors, including the duration of follow up, the setting (e.g., rehabilitation centre is likely to report a higher incidence than an intensive care unit) and whether the diagnosis is based on imaging results or clinical symptoms (e.g., many cases go unreported, particularly in SCI patients, as often NHO is only detected when causing pain and reducing mobility) [3,17,26–28].

The formation of NHO typically occurs within 1 to 3 months of CNS injury and is associated with warmth, swelling, erythema and soft tissue breakdown, which makes it difficult to diagnose as these symptoms share similarities with other inflammatory conditions including sepsis, cellulitis, deep vein thrombosis and osteomyelitis [12,23,29–33]. NHO typically forms between the muscle planes surrounding joints, however, formation can also occur within the muscle or joint itself [12]. The most common site of NHO formation is the hip, although it also frequently seen around the elbow, knee or shoulder, while joints of the wrist, ankle, hand and feet are rarely effected [3,9,23,34,35]. In approximately 20% of NHO patients, bone formation progresses to cause nerve impingement/entrapment and contractures, which can be extremely debilitating by reducing range of motion and causing severe pain [9]. Following SCI, NHO usually occurs below the level of CNS lesion and the severity of NHO has been correlated to the completeness of the SCI lesion [36,37]. In addition, there is some evidence that SCIs to the thoracic and cervical regions are more likely to progress to ankylosis than lumbar injuries [18].

Although NHO is frequently observed following CNS injuries to civilians, evidence accumulated over the past two decades suggests that NHO is particularly common following combat-related trauma, specifically blast-related TBI (bTBI) [22,38]. During the recent conflict in Iraq and Afghanistan it is estimated that 78% of injuries were due to an explosive mechanism, hence, bTBI has been termed the "signature wound" of these military operations [39]. Blast generates high-energy supersonic pressure waves, electromagnetic pulses, heat, and toxic gases, which can cause central and peripheral injuries that may trigger NHO [40–42]. Although the exact prevalence of NHO following bTBI is unclear, due to a limited number of studies, recent reports suggest that the incidence may be significantly higher than following non blast-related TBIs [22,38]. A recent study that examined the prevalence of HO following combat-related trauma in patients who underwent at least one orthopaedic procedure on an extremity and tended to be severely injured, reported that 68% of patients who had sustained injuries due to blast exposure without TBI went on to develop HO while, 86% of bTBI patients developed NHO [22]. While these finding indicate that HO development in the absence of neurological injury is still common in blast victims, univariate analysis on this cohort revealed that a bTBI was a strong predictor of the risk of HO [22]. A blast mechanism of injury has also been associated with similarly high incidence of HO in combat-related amputees [38]. Despite these findings, further large-scale studies are required to determine the exact prevalence of blast-induced HO and to examine the relationship between bTBI and NHO.

3. Pathogenesis and pathobiology

The cellular and molecular mechanisms by which NHO forms are still being elucidated, although it is generally agreed that the process is initiated following a concomitant central and peripheral injury to stimulate bone formation at the site of the peripheral injury via endochondral ossification [16,31,43]. Injury to the CNS and peripheral tissue initiates an inflammatory cascade, with inflammatory cells including neutrophils, lymphocytes and macrophages, as well as dead and dying native cells thought to release a range of growth factors and cytokines that stimulate fibroblastic proliferation and collagen deposition at the peripheral injury site [44]. Inflammatory lesions around/within muscle and joints that later transition to bone are profoundly hypoxic [45,46]. This hypoxic microenvironment is thought to trigger the release of endogenous factors that are responsible for the formation of mesenchymal condensations at the peripheral injury site and infiltration of mesenchymal cells and osteoprogenitor cells, which due to hypoxia differentiate into chondrocytes [45,47]. These chondrocytes enter an intense phase of cellular division before becoming hypertrophic and secreting a cartilaginous matrix [46,48,49]. Recent human and animal studies suggest that, in response to trauma, brown adipocytes may act to reduce oxygen tension creating a hypoxic environment that promotes chondrocytic differentiation and hypertrophy [50,51]. Following cartilage deposition, remodelling of the matrix is thought to result in the release of angiogenic factors that further promote vascular invasion and initiate sufficient oxygen tension necessary to promote osteoblastic differentiation [49,52,53]. At regions where oxygen tension is sufficient, typically around the periphery of the lesion [54], bone formation occurs as cartilage is removed and osteoblasts deposit osteoid on the remnants of the cartilaginous template which later becomes mineralized [49,55]. Over time the initial woven bone formed remodels into mature lamellar bone that possesses Haversian canals, blood vessels and a marrow cavity making it unique from other conditions involving ectopic mineralization such as dystrophic calcification [49,54–56].

4. Current treatments

The only effective therapy currently used for established NHO is surgical excision [3,23]. Historically, surgical excision was usually delayed for several months following HO development, primarily to avoid significant haemorrhage during surgery, reduce the perceived risk of post-operative recurrence of NHO, and to ensure that maximum neurological recovery had occurred as spasticity and reduced functional movement have been associated with recurrence [57–59]. More recent studies have, however, indicated that there is no relationship between the timing of excision and NHO recurrence, and that there is no association between the severity of neurological sequelae and risk of recurrence following TBI and SCI [3,23,60,61]. In fact, recent studies have shown that delaying surgery can result in poorer outcomes (i.e., less range of motion), while in ankylosed joints delaying surgery can lead to immobilisation-induced osteopenia/osteoporosis, which increases the risk of further complications such as peri-operative fracture [23,58,62]. Additionally, reduced range of motion prior to surgery may induce cerebral changes including atrophy of motor areas, which has the potential to inhibit recovery of range of motion following surgery [63]. Moreover, numerous lines of evidence indicate that early surgical excision enhances functional outcomes and is not a factor in the recurrence of NHO [3,23,60,61]. Recent reviews by Almangour et al., and Genet et al., recommend that surgical resection of TBI- and SCI-induced NHO as soon as comorbid factors are controlled and NHO is constituted for excision [23,61]. However, surgical excision of NHO is difficult and often problematic, particularly when ectopic bone entraps nerves and blood vessels. In addition, surgical intervention results in recurrence of NHO in up to 20% of cases as well as additional complications such as peri-operative fracture and infection [12,13].

Inflammation is thought to play a key role in the development of NHO, therefore some have hypothesized that treatment with non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the incidence and impact of NHO [64,65]. Preliminary studies in SCI patients have reported that patients treated with indomethacin or Rofecoxib had a lower incidence of NHO [64,65], while patients treated with indomethacin who did develop NHO presented with symptoms later than did control patients [64].

Bisphosphonates have also been used to treat TBI and SCI patients with NHO. The commonly used bisphosphonate, etidronate, inhibits the formation of bone mineral, however organic matrix deposition is unaffected and bone formation usually recurs if treatment continues for <6 months following injury [29]. Severe TBI patients treated with etidronate beginning at seven days post-injury had a lower incidence of NHO when compared to controls [66]. In addition, in SCI patients with scintigraphy detected NHO, those treated with etidronate had a

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