Heterotopic Ossification in Neurorehabilitation

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ABSTRACT

Neurogenic heterotopic ossification (NHO) involves deposition of bone in extraskeletal tissue in the setting of a neurological disorder, and its pathophysiology is incompletely understood. NHO can lead to significant disability and functional impairment. NHO initially manifests as pain and joint stiffness. Early diagnosis requires appropriate suspicion and imaging studies to detect the uncalcified collagen matrix that forms in the early stages of NHO. If diagnosis is made in the early phase of NHO, progression may be halted with bisphosphonates, indomethacin or radiation therapy. If NHO progresses to its final stages without intervention, it may restrict joints and render them dysfunctional. Surgical treatment of NHO may restore function, but complications may occur, and prophylaxis and aggressive rehabilitation are essential. 

KEYWORDS: Heterotopic ossification, bisphosphonates, indomethacin, radiation therapy, rehabilitation

INTRODUCTION

Neurogenic heterotopic ossification (NHO) refers to the aberrant formation of bone in extraskeletal tissue in the context of a neurological condition. NHO is one of the most common complications associated with traumatic spinal cord (SCI) and brain injuries (TBI), with an incidence of over 50% in SCI and 20% in TBI patients. NHO may also develop with other neurological conditions including stroke, cerebral anoxia, Guillain-Barre syndrome, tumors and infections. Various risk factors have been associated with the development of NHO, including prolonged immobilization, muscle spasticity, and a long hospital length of stay. NHO has a tendency to develop around larger joints, particularly the hip and knee; however, it may develop near any joint, including the shoulders, elbows, and spine. The exact pathophysiology that causes NHO formation is not completely understood.

Pathophysiology

NHO is thought to be caused by the induction of pluripotent mesenchymal stem cells by signaling factors that are present in patients with neurologic conditions or trauma. Recent evidence suggests that these mesenchymal cells originate from muscles and their differentiation is dependent on soft tissue macrophages. The resulting osteogenic cells lead to aberrant bone formation in extraskeletal tissue. Many humoral factors have been implicated, particularly BMP-4 and substance P, however, none have been definitively proven to be the primary culprit in NHO.

Several studies have investigated the role of peripheral nerves in NHO. Campos da Paz et al. suggested that altered proprioception could lead to tissue irregularities that predispose patients to NHO. Salisbury et al. demonstrated that sensory nerves are stimulated by BMP-2, an osteogenic factor that induces a neuroinflammatory response and leads to the proliferation and release of osteogenic cells. NHO can be a painful condition, but the etiology of the pain is unclear. Local factors such as substance P and neuropeptides released in local soft tissues are thought to stimulate peripheral nerves, leading to the perception of pain.

NHO formation occurs in three phases. First, immature NHO is deposited in extraskeletal tissue. This primarily comprised of well-organized collagen fibers with minimal calcification. Second, an inflammatory process leads to the vascularization of this tissue, which allows osteogenic cells to further induce immature bone formation. During the final phase, remodeling and maturation occurs. This last phase is associated with mature bone and minimal activity on 99m-technetium bone scanning.

Diagnosis

Early NHO manifests as joint stiffness, skin erythema, swelling and pain. Without appropriate suspicion, the diagnosis of early NHO is elusive because the condition is not evident on radiographs or computed tomography scans. Patients with neurological disabilities are at high risk of deep venous thromboses (DVTs), and this condition should be excluded. Once critical diagnoses like septic joint, tumor, and deep venous thromboses are ruled out, a patient at high risk of developing NHO must have further studies to support the diagnosis.

Early diagnosis of NHO is important because it allows for interventions that may stop its progression. Early diagnosis can be accomplished with 3-phase 99m-technetium bone scanning, MRI or ultrasonography. Bone scans may detect lesions suspicious for NHO in a high-risk patient; however, the specificity for making the diagnosis is low and further testing is required to prove its efficacy. Similar to bone scans, MRI is able to reliably detect NHO but the specificity is low.
Recently, it has been shown that ultrasound has proven to be a reliable method of diagnosing NHO in its early phases.\textsuperscript{14} Laboratory studies are not diagnostic for NHO, however, they may help identify the presence of NHO in its early inflammatory phase. Simultaneous elevations of phosphorus and alkaline phosphatase have been associated with NHO.\textsuperscript{15} Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are typically elevated in the acute inflammatory phase of NHO and normalize once this phase is over.\textsuperscript{16}

**Treatment**

Research studies of prophylaxis with bisphosphonates and indomethacin to prevent heterotopic ossification have shown similar efficacy.\textsuperscript{18-20} These drugs target the early inflammatory phase of NHO. Generally, indomethacin is not tolerated as well as bisphosphonates, with adverse effects being reported in up to 31% of patients.\textsuperscript{20} Although bisphosphonates are effective in NHO prophylaxis, they are up to six times more costly.\textsuperscript{20}

In the early stages of NHO, radiation therapy has also been effective in halting the progression of NHO.\textsuperscript{12} Unlike bisphosphonates and NSAIDS, which target the inflammatory cascade that activates osteogenic cells, radiation therapy inactivates the pluripotent osteoprogenitor cells that have been mobilized by the inflammatory cascade.\textsuperscript{21} In patients diagnosed with early NHO as well as those who had NHO resection and radiation therapy, progression or recurrence was prevented in over 70%.\textsuperscript{22}

In the late stages of NHO, associated with functional impairment and pain, excess bone must be excised surgically (figure 1).\textsuperscript{23} It has been reported that excision should not be performed until the growth and maturation phases have ended, which has been estimated to be over one year for NHO related to SCI and over 1.5 years for TBI.\textsuperscript{12,24}

However, despite confirmation of the end of the growth or maturation phases of NHO, recurrence rates of NHO have been reported in over one-third of patients who undergo excision.\textsuperscript{12,25}

Fortunately, surgical resection that is combined with prophylactic bisphosphonates and radiation therapy has significantly reduced the recurrence of NHO.\textsuperscript{26} This suggests that the risks and benefits of waiting to excise NHO until the maturation phase must be weighed with the risk and benefits of earlier excision. Earlier excision may require less surgery if appropriate prophylaxis is used to prevent recurrence, as it may avoid the soft tissue contractures that often develop with NHO and the resulting immobilization.

Regardless of the phase of NHO or intervention utilized for prophylaxis or treatment, physical and occupational therapy have a significant role in the management of NHO. Physical therapy has not been proven to independently prevent the formation of NHO.\textsuperscript{12} However, range-of-motion exercises are important in preserving joint function by preventing soft tissue contractures.\textsuperscript{12} In the late stages of NHO, where function is impaired by a restricted joint, excision is generally combined with postoperative prophylaxis and a rehabilitation program to optimize function and prevent recurrence.\textsuperscript{27}
CONCLUSION

NHO deposition of bone in extraskeletal tissue is a disabling condition that is common following SCI, TBI, and other neurological conditions. Early diagnosis requires appropriate suspicion and imaging studies. If the diagnosis of NHO is made in the early phase, progression can sometimes be halted with bisphosphonates, indomethacin or radiation therapy. If NHO progresses to its final stages without intervention, it could restrict joints and render them dysfunctional, ankylosed, and painful. In cases where excision is performed to restore function, prophylaxis and regimented rehabilitation are required to maintain function and improve outcomes.

References


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