

Heterotopic Ossification of the Hip

Pathogenesis: The basic defect in HO is inappropriate and rapid metaplastic osteogenesis which results in the formation of lamellar corticospongiosal bone. However, both the specific pathophysiology and etiology of HO remain unclear. What induces precursor cells to go through metaplasia and initiate osteogenic activity is still unknown. Similarly the identity of these precursor cells has not been established. Further, it is not known why heterotopic ossification does not materialize in all cases with similar conditions. It seems, though, that there are three requisite conditions for HO to occur. In addition to an osteogenic precursor cell, there must be an inducing agent and a tissue environment that is permissive of osteogenesis.

It appears that non-circulating pluripotent mesenchymal cells are most likely the cells which differentiate to become osteoblastic stem cells. This occurs very soon after injury, within 16 hours after experimentally induced trauma to mice femurs. This suggests that significant pathophysiological events may be occurring in the immediate post-traumatic period, while patients are still receiving acute care.

Two possible candidates which act as inducing agents have been established. Through *in vitro* research it has been established that demineralized bone matrix can induce new bone formation via an osteoinductive protein released from the matrix, now known as bone morphogenic protein (BMP). Additionally, prostaglandins have been implicated as inducing agents.

Certain tissues (spleen, liver and kidney) suppress bone induction while others (muscle and fascia) permit experimental induction of bone. Local factors present within the permissive tissues may further predispose them to HO. These are hypoproteinemia, venous thrombosis or hemostasis, (local) infection, decubitus ulcers and (micro) trauma. Any of these factors may lead to tissue damage and subsequent inflammatory reaction, resulting in edema and tissue hypoxia, further disposing the tissues to heterotopic bone formation. Immobilization can further tissue hypoxia, also contributing to the onset of osteogenesis.

Additional theories of pathogenesis have been put forth to explain neurogenic HO (NHO) as it is known to occur in regions of the body without obvious soft tissue damage, e.g. after spinal cord injury. One theory suggests that damage to the intermedio-lateral sympathetic columns of the traumatized spinal cord might predispose to NHO through autonomic dysregulation. Secondary to an altered balance within the autonomic nervous system, a diversity of metabolic and vascular changes may occur.

The causative agent of heterotopic bone formation has been debated in the literature since the late 1800s. Results from several recent case studies suggest that vigorous passive exercises increase the incidence of HO, but also that a longer time interval between the injury and the beginning of well-dosed passive movement exercises, especially in neurological cases, enhances the risk of HO. These results have also been supported by animal studies. Moreover, biological, biochemical, and biomechanical investigations have established that (micro)trauma and mechanical stress to the musculotendinous apparatus may arise either from vigorous passive exercises or from loss of mobility and muscle imbalance causing peak pressure on soft tissue areas. Mechanical stress causes local microtrauma that may induce ossification either indirectly through an inflammatory response or directly by releasing osteoblast-stimulating factors. In cases of HO accompanied by SCI, the condition for ossification might be further established by the highly “vascular” state of the paralyzed area and the high likelihood of concomitant use of anticoagulants, which may predispose to hematoma and secondary NHO, particularly during the

rehabilitation phase after SCI. Current speculation is that (forced) passive movements following a period of immobilization may easily result in shear and tear of soft tissues leading to an increased risk of developing NHO.

In summary, the common features in all the conditions in which HO is seen are immobilization due to trauma, surgery, or forced therapeutic rest, followed by mobilization with exercise or spasticity. Whether tissues ossify may depend on a fine balance of osteogenic and osteo-inhibitory influences acting both locally and systemically.

Although the mechanisms underlying the development of HO are still not fully elucidated, numerous risk factors have been identified. These can be grouped according to three parameters: patient-related, injury-related, and treatment-related factors. Patient-related factors include male gender (although this may be more a factor of the higher incidence of SCI occurring in the male population), a history of HO after previous hip surgery, bilateral hip disease, hypertrophic osteoarthritis with massive acetabular osteophytes, poor preoperative range of motion at the hip in total hip replacement, fever at the time of surgery, and the presence of other bone-forming disorders such as diffuse idiopathic skeletal hyperostosis, ankylosing spondylitis, and Paget disease. Incidence of HO has no relationship to racial group.

Injury-related risk factors include trauma and full-thickness burns. Treatment-related factors include revision arthroplasty, tissue hypoxia, circulatory stasis, postoperative immobilization with limitation of joint movement, bone demineralization from prolonged bed rest or assisted ventilation, postoperative dislocation of a hip prosthesis in the first week after surgery, postoperative fever lasting more than 5 days, and postoperative hematoma.

Finally, there are specific risk factors for NHO with spinal cord or brain injury. In NHO accompanied by spinal cord injury four risk factors have been identified, including age (older than 30 years), completeness of injury, presence of spasticity, and coexistence of pressure ulcers. These risk factors appear to be additive. The greater the number of risk factors, the higher the incidence of the disorder. Also, HO is less likely to occur in patients whose neurological level of lesion is in the lumbar region. In traumatic brain injury heterotopic ossification seems to be related to the severity of the injury, coma lasting greater than 2 weeks, proximity of fracture to long bones and significant spasticity. HO is rarely seen in flaccid limbs.

Epidemiology: Occurrence rates of HO vary depending on the associated injury. In patients with spinal cord injuries, HO is found in 20-30% of cases; however, limitation of joint motion occurs in 18-35% of these cases. Following closed-head injuries the incidence of HO is 10-20% with approximately 10% of these patients demonstrating severe restriction of joint motion (not limited just to the hip). Lower rates are reported among CVA patients. In the traumatic brain injured and the spinal cord injured populations, studies have shown that in those diagnosed with HO, 10% to 16% progress to complete joint ankylosis. After total hip replacement, HO has a reported incidence of 8-90%, although it is clinically significant in only 2-7%. Following internal fixation of acetabular fractures, up to 50% of patients develop HO and in nearly 50% of these cases not treated prophylactically, the HO causes disablement.

Isolated HO can occur at any age but is rare in very young children. Posttraumatic HO is, not surprisingly, most common in young athletic persons. Neurogenic HO is less common in children than among adults and although the clinical symptoms in children are similar to those reported in adults, spontaneous regression of neurogenic HO is more often reported in children and young adults than in older adults.

Diagnosis: As stated earlier, secondary to early induction of osteoblastic stem cells, the initial pathophysiological events setting up the possibility of heterotopic bone formation may occur in the immediate post-trauma period. However, the onset of actual heterotopic bone formation usually occurs approximately 2 weeks after injury, although symptoms may not be noted for 8 to 10 weeks. HO is primarily diagnosed based on clinical signs and likelihood. Symptoms similar to those in trauma, inflammation, or tumor occur in the early stages and include peri-articular swelling, erythema, localized tenderness and increased temperature. Additionally, sudden decrease in range of motion is the most common finding and is often the earliest sign of HO. Fever and malaise may also be present. Pain may or may not be present, depending on whether sensation is intact. In patients with NHO, limb spasticity may be enhanced. These early symptoms must be differentiated from arthritis, thrombophlebitis, DVT, cellulitis, soft-tissue hematoma, complex regional pain syndrome and soft-tissue tumor. Thrombophlebitis or DVT may be the most difficult differential diagnosis. Upon visual inspection, the edema of thrombophlebitis/DVT is less localized and more generalized in the lower limbs than in HO. A definitive differentiation can only be made, however, through the use phlebography or ultrasound, especially during the early stages and when it is too early to find radiological evidence of HO.

Laboratory results may show a transient depression in the serum calcium level 1 week after initial insult and an acute elevation in the serum alkaline phosphatase (SAP) level in as little as 2 weeks after insult and on average 7 weeks before the first clinical signs of HO become apparent. Elevated SAP presumably reflects intense osteoblast activity in the local lesions of heterotopic ossification and is associated with clinically significant heterotopic ossification. SAP consists of a series of iso-enzymes which are sensitive, but non-specific indicators of HO. When new bone is actively deposited, the SAP levels are elevated. As soon as the ossification process has stopped, the enzyme levels return to normal. Since SAP levels are non-specific in that they are found in various tissues, they only become strong indicators of HO when they are associated with the clinical signs previously described.

Three-phase 99m Technetium bone scan is the current “gold standard” for earliest detection of HO. In the early stages of HO, the bone formation mainly consists of osteoid that shows a high uptake of osteotropic radionuclides which is readily detectable by bone-scanning. The first phase of the three-phase scan is the period immediately after the intravenous injection of the radionuclides and detects areas of increased blood flow, which is an early indicator of an inflammatory process (the dynamic blood flow phase). The second phase (the static blood pool phase) identifies areas of blood pooling several minutes after the injection. The third phase (the static bone phase) determines the degree of osseous uptake of the labeled radionuclides several hours after the injection. The first two phases of the bone scan are able to detect HO as early as 2.4 weeks after injury and are followed by a positive static bone phase 1-4 weeks later. Compared to plain radiography, bone scanning is a more sensitive diagnostic test for early HO, but radiography is more specific. A disadvantage of the bone scan is its low specificity leading to potential difficulty in discriminating HO from other inflammatory, traumatic, or degenerative processes of the skeleton, e.g. fracture, bone tumor, metastasis, or osteomyelitis which all show increased osteoblastic activity.

Ultrasonography is gaining ground as a preferred initial imaging modality for patients with clinically suspected HO and for differentiating HO from DVT, a developing pressure sore, infection, or tumor. The unique pathological evolution of the ossification can be monitored by sequential sonographic assessment. Although ultrasound can be highly specific and sensitive for

diagnosing HO, these benefits depend strongly on the experience of the radiologist.

Tissue diagnosis by biopsy is not done because of the risk of exacerbating the disorder by resection of an immature lesion. Similarly, CT scanning and MRI are rarely used in the early detection of HO but can be of great benefit in developing a plan for surgical resection of HO.

Surgical Procedure: Surgical resection of HO is often a difficult procedure and is considered only in refractory cases not satisfactorily relieved with conservative methods. Indications for surgery include joint immobility causing difficulty in patient positioning, hygiene, ambulation or daily activities; ankylosed joints resulting in pressure sores or skin breakdown; reduction in spasms; and conditions in which HO contributes to peripheral neuropathy.

Traditional thought is that the surgery must be delayed until the bone scan ratio is at steady state and serum alkaline phosphatase (SAP) returns to a normal level, which is usually 12-18 months after injury. More recently, several investigators have published good results of early wedge resection of HO that has not reached maturity. Wedge resection of HO is recommended in lieu of wide resection as the latter often leads to extensive bleeding, wound infection, prolonged immobility and in rare instances necessitates hip disarticulation or higher level amputations. Other risks associated with resection include fracture, ankylosis, pressure ulceration and painful arthrosis or pseudarthrosis. These complications are not uncommon and carry high morbidity.

Success of wedge resection appears to be somewhat dependent on location of the HO. Anterior bone resection usually meets with excellent results for improving hip ROM. Medial bone resection also provides good results with ROM. Early percutaneous or open adductor myotomy and obturator neurectomy are useful in maintaining hip abduction. The posterior bone formation about the hip is the most serious. Since hip flexion contractures are almost always present, resection of posterior ectopic bone may not always be helpful. In this case, a proximal femur extension osteotomy is performed to obtain more range.

A controversial alternative to surgical resection is forceful manipulation under anesthesia. It has been found to be particularly useful in HO with brain injury. Its efficacy for enhancing range of motion versus aggravating and contributing to the HO process is still being studied. It is performed as the heterotopic bone is growing to maintain range and to prevent ankylosis. Repeated manipulations may be warranted if neurologic status improves. If it does not, joint ankylosis may be inevitable. Joint manipulation may also be desirable to place the affected joint in a more functional position when ankylosis is inevitable. Postmanipulation care includes range of motion, use of a continuous passive motion (CPM) machine and 24-hour positioning regimens.

Preoperative Rehabilitation: Since surgical intervention is chosen only in refractory cases, rehabilitation consists of efforts to avoid surgery and is considered as a first line treatment modality. Rehabilitation efforts have included monitoring patients for signs suggestive of HO, administering range-of-motion exercise, intervention in seating systems and bed positioning, turning, the use of physical agents, early mobilization of patients, and patient and/or family education.

Through daily hands-on interventions with patients at risk for HO, physical therapists may be the first to become suspicious of the possible onset of HO. In fact, in a retrospective study of 1209 patients with SCI, it was primarily physical therapists that were first to suspect the onset of HO. Physical therapists should observe at-risk patients for decreased range of motion

and for the other symptoms suggestive of HO previously mentioned: peri-articular swelling including the distal leg in HO at the hip, erythema, warmth, localized tenderness, pain and increased spasticity. Early observation of these signs may assist in the early diagnosis of HO, thereby increasing the ability to manage it pharmacologically, without eventual surgical intervention.

There still is no conclusive evidence based on random controlled studies in humans regarding the appropriateness of range of motion exercises to prevent HO. In fact, most recently, van Kuijk and Silver emphasize the power of clinical observation in determining the benefit of range-of-motion exercises to prevent HO, despite the paucity of evidence-based support. From these observations they make strongly stated recommendations that early range-of-motion exercises are beneficial in the prevention and treatment of HO. Some have even called range-of-motion exercises “the mainstay of HO prevention.” These exercises are believed to work by inhibiting fibroblast activation and, thereby, preventing muscle contractures. When gentle and cautious passive movements of the large peripheral joints are started and maintained from the day of spinal cord injury, it is believed that the joint capsules are kept as supple as possible, muscles will not easily shorten and contractures will not readily develop, so that HO may be prevented. On the other hand, if a paralyzed extremity is not moved immediately after onset of injury, exactly the reverse occurs. Joint capsules, muscles, ligaments and fascia shrink and adhesions develop between various soft tissue compartments. Once these changes have occurred, subsequent passive movements result in shear and tear of the soft tissue and if this is large enough, it triggers an abnormal process of repair.

Once heterotopic bone begins to form, the role of physical therapy for HO management remains even more controversial. Secondary to the inflammatory component of HO, many argue that the therapist should not attempt to mobilize the involved joint directly during the active stage of HO, as this might cause further inflammation or trauma and so increase the amount of bone formation. Based on clinical evidence, Chantraine and Minaire recommend that mobilization of those with SCI should be replaced by placing patients in alternating positions of 90° of the hips and knees and that the position be changed every three hours to maintain sufficient range of motion at both joints for functional independence. Once the diagnosis of traumatic heterotopic ossification becomes definitive, it is recommended that active range of motion exercise be continued within the pain-free range.

With regular turning and correct positioning, spasticity is greatly reduced and the development of pressure sores prevented. Thus two significant, known risk factors can be eliminated if an appropriate turning and positioning program is carefully followed. Prone positioning relieves pressure from the most common sites of decubitus ulcer formation and diminishes the risk of flexion contractures of the hips, thus reducing the likelihood of HO developing on their anterior aspect. It can also help to inhibit extensor spasticity.. Sitting the brain-injured patient out of bed regularly may also help to reduce spasticity. From extensive rehabilitation experience, Davies asserts that it is extremely rare to find HO in brain-injured patients who have been sat out of bed while still in coma and stood with the help of knee-extension splints.

For optimal reduction of spasticity and prevention of decubitus formation, the patient should be turned at least every two hours. When working with comatose patients, at least two caregivers are required to turn adult patients in order to eliminate all danger of traumatizing the limbs. Turning such a patient alone may easily result in a limb being pulled into an extreme range of motion resulting in minor trauma which is possibly a contributory factor in HO. When

the patient is being turned, the limbs should be flexed in order to shorten the lever arms and then gradually eased into the corrected position once in side-lying.

Finally, the importance of early mobilization in a wheelchair cannot be stressed enough. In the case of a complete neurological lesion when no recovery of lost function can be expected, patients should be allowed out of bed as soon as the pain at the site of spinal fracture and the condition of concomitant injuries no longer preclude mobilization. In those with incomplete spinal cord lesions, mobilization should begin as soon as the danger of increase in collapse of a crushed vertebral body or of dislocation is over. Early wheelchair mobility decreases the duration of immobilization which is believed to be a primary risk factor of HO.

Chantraine and Minaire report that various physical agents have been tried, including ultrasound, iontophoresis, and cryotherapy, all as adjunctive therapy against inflammation. However, they give no evidence of the efficacy of these modalities.

Once hip range of motion becomes limited and an increase in spasticity secondary to neurogenic HO develops, the patient's positioning may be compromised. The physical therapist should evaluate and recommend changes to seating (if the patient mobilizes in a wheelchair) and to positioning in bed (for bedridden patients) to prevent the risk of pressure sores and related pain complaints. The decreased range of motion at one hip causes body weight to be unequally distributed between the ischial tubera, making it possible for pressure ulcers to evolve usually on the side contralateral to the hip affected by neurogenic HO.

Finally, patients at risk for HO need to be educated about the possible complication of HO and its indicators. If the condition develops, patients need to be informed thoroughly about the condition and the various means of treatment. A safe passive or active-assisted ROM program needs to be presented to the patient and family members to prevent loss of motion, contractures, and possible loss of function. Family members or other caregivers must be educated to avoid overly aggressive ranging of the patient's limbs in order to minimize the possible risk of initiating HO.

POSTOPERATIVE REHABILITATION

Little mention is made of post-surgical care in the literature other than the administration of disodium etidronate and prophylactic antibiotics given pre-operatively and post-operatively for approximately 7 days or NSAIDs and/or radiotherapy. These therapies are warranted after surgery, as surgically resected HO has a high rate of recurrence. Post-operative radiation has been reported to decrease the recurrence of HO after surgical resection in SCI patients, but no controlled studies are available. Both radiation and indomethacin seem to be effective in preventing HO occurrence after total hip replacement.

When mention is made of rehabilitation, however, there is little agreement about when it should be initiated and what it should include. Furthermore, evidence-based research regarding post-surgical rehabilitation of HO at the hip is non-existent.

In one surgical case study of HO at the hip with concomitant SCI, the physician advocated an intensive rehabilitation program post-operatively to prevent recurrence of the ossification by unopposed spasticity of the patient's hip extensors. No description was given, however, of the interventions comprised by the recommended rehabilitation program.

In another series of hip resections performed on patients with paraplegia, strict timing

and cautious use of movement exercises were employed. No passive movements were allowed during the first 14 days following resection. From day 15 forward, continuous passive motion was used to achieve suitable flexion for wheelchair mobility (70° to 90°). Passive motion exercises were continued once patients were mobilizing themselves in wheelchairs.

One author advocates for ROM exercises to begin as early as 48 to 72 hours after surgery in patients with HO associated with burns. Another suggests ROM exercises should begin one week after surgical resection of NHO associated with traumatic brain injury. Neither cites evidence-based research to support these recommendations.

According to Anderson with regards to surgically resected HO with brain injury, passive ROM and CPM should also be initiated 3 to 5 days postoperatively to keep the joint surfaces lubricated. When the patient is cleared by the surgeon for weight-bearing activity, motor re-education and strengthening in function should begin. Commonly, functional hip ROM is obtained after surgical resection; however, it is not uncommon for the patient to revert back to compensatory postures and movements after the bone has been resected. Motor re-education and functional strengthening are critical so that the patient may become more efficient with movement and function. Anderson also states that 24-hour positioning is important for maintaining hip range of motion. Although Anderson provides the most detailed guidelines for post-operative care, no evidence-based research is provided to support these recommendations.

Selected References:

Lal S. Heterotopic ossification. In: Green D, ed. *Medical Management of Long-Term Disability*. Boston:Butterworth-Heinemann, 1996:95-113.

van Kuijk AA, Geurts ACH, van Kuppevelt HJM. Neurogenic heterotopic ossification in spinal cord injury. *Spinal Cord*, 2002;40:313-326.

Damanski M. Heterotopic ossification in paraplegia: a clinical study. *The Journal of Bone and Joint Surgery*, 1961;43 B:286-299.

Singer, BR. Heterotopic ossification. *British Journal of Hospital Medicine*. 1993; 49:247-255.

Riklin C, Baumberger M, Wick L, et al. Deep vein thrombosis and heterotopic ossification in spinal cord injury: a 3 year experience at the Swiss Paraplegic Centre Nottwil. *Spinal Cord*. 2003;41:192-198.

Crawford CM, Varghese G, Mani MM, Neff JR. Heterotopic ossification: are range of motion exercises contraindicated? *J Burn Care Rehabil*. 1986;7:323-327.

Michelsson JE, Granroth G, Andersson LC. Myositis ossificans following forcible manipulation of the leg. *Journal of Bone and Joint Surgery*. 1980; 5:811-815.

Izumi K. Study of ectopic bone formation in experimental spinal cord injured rabbits. *Paraplegia*. 1983;21:351-363.

Smoeckx M, De Muyenck M, Van Laere M. Association between muscle trauma and heterotopic

ossification in spinal cord injured patients: reflections on their causal relationship and the diagnostic value of Ultrasonography. *Paraplegia*. 1995;33:464-468.

van Kuijk AA, Geurts ACH, van Kuppevelt HJM. Letter to the editor. *Spinal Cord*.2003;41:423-424.

Schafer SJ, Schafer LO, Anglen JO, Childers M. Heterotopic ossification in rehabilitation patients who have had internal fixation of acetabular fracture. *Journal of Rehabilitation Research and Development*. 2000; 37: 389-393.

Goldman J. Heterotopic ossification in spinal cord injuries. *Physiotherapy*.1980; 66:219-220.

Anderson D. Management of decreased ROM from overactive musculature of heterotopic ossification. In: Montgomery J, ed., *Physical Therapy for Traumatic Brain Injury*. New York: Churchill Livingstone, 1995:79-97.

Blount PJ, Bockenek WL. Heterotopic ossification. In: Frontera WR, Silver JK eds., *Essentials of Physical Medicine and Rehabilitation*. Philadelphia: Hanley & Belfus, Inc., 2002:569-574.

Garland DE. Heterotopic ossification in traumatic brain injury. In: Ashley MJ and Krych DK, eds. *Traumatic Brain Injury Rehabilitation*, Boca Raton: CRC Press, 1995:119-129.

Guo Y, CollacoCR, Bruera E. Heterotopic ossification in critical illness and cancer: a report of 2 cases. *Arch Phys Med Rehabil*. 2002;83:855-859.

van Kuijk AA, van Kuppevelt HJM, van der Schaaf DB. Osteonecrosis after treatment of heterotopic ossification in spinal cord injury with the combination of surgery, irradiation, and an NSAID. *Spinal Cord*. 2000;38:319-24.

Freebourn TM, Barbert DB, Able AC. The treatment of immature heterotopic ossification in spinal cord injury with combination surgery, radiation therapy and NSAID. *Spinal Cord*. 1999;37:50-53.

Jamil F, Subbarao JV, Banaovaac K, et al. Management of immature heterotopic ossification (HO) of the hip. *Spinal Cord*. 2002;40:388-395.

Garland DE, Razza B, Waters RL. Forceful joint manipulation in head-injured adults with heterotopic ossification. *Clinic Orthop*. 1982;169:133-8.

Silver, J. Letter to the editor. *Spinal Cord*.2003; 41:421-422.

Ellerin BE, Helfet D, Parikh S, et al. Current therapy in the management of heterotopic ossification of the elbow: a review with case studies. *Am J Phys Med Rehabil*. 1999;78:259-271.

Davies PM. *Starting Again: Early Rehabilitation after Traumatic Brain Injury or Other Severe Brain Lesion*. Berlin: Springer-Verlag, 1998: 361-381.

Chantraine A, Minaire P. Para-osteo-arthropathies. *Scand J Rehab Med*. 1981;13:31-37.

Meiners T, Abel R, Bohm V, et al. Resection of heterotopic ossification of the hip in spinal cord injured patients. *Spinal Cord*. 1997;35:43-45.