Heterotopic Ossification (HO)

I. Definition, Assessment, Diagnosis
   A. Definition.
      1. Heterotopic ossification (HO) is a process by which ectopic bone is formed in the soft tissue surrounding peripheral joints. Osteoprogenitor stem cells lying dormant in the surrounding soft tissues with the proper stimulus (such as hip surgery, spinal cord injury (SCI), and stroke) differentiate into osteoblasts and cell lines involved in bone formation. These cells then calcify and form well-organized bone over a several month period.
         a. Previous studies suggest that ectopic bone formation require three conditions: osteogenic precursors, an inducing agent, and an environment permissive to osteogenesis. There is likely a connection between stimulation of mesenchymal cells followed by osteoprogenitor maturation and osteoblast activation.
         b. It is thought genetic predisposition, such as HLA B27, combined with presence of osteoblast stimulating factors and prostaglandins contribute to ectopic formation. Studies show there are increased stimulating factors and osteoblastic activity in animals with SCI.
         c. Though the relationship between central nervous system and bone is not completely understood, neurotransmitters likely have an effect on bone metabolism.
         d. Phagocytic macrophages, rather than osteoclasts, recruited in inflammatory muscle are also thought to be responsible for triggering neurogenic HO development. Targeting phagocytic macrophage recruitment is a promising therapeutic approach to prevent neurogenic heterotopic ossification (NHO).
         e. These results supported the previous finding that naive muscle progenitor cells are capable of mineralizing secondary to inappropriate CNS signaling that reprograms progenitor cells to osteogenesis instead of muscle repair.
            i. Risk factors. Heterotopic ossification can be either acquired or neurogenic.
            ii. Acquired HO, which is more common, can occur after any type of musculoskeletal trauma or injury, such as total hip arthroplasty, fractures, burns or hip dislocations.
            iii. Neurogenic HO is most common in patients with SCI, traumatic brain injury (TBI), and less commonly, stroke.
            iv. Reported to occur in 16-53% of patients after SCI. Most common locations are hip, knee, shoulder, and elbow.
v. Incidence after TBI ranges from 11-28% commonly affected by immobility, spasticity, and fractures. Dysautonomia may also be a risk factor.

vi. Numerous sources have investigated potential factors contributing to development of HO.

vii. A case-control study on patients with traumatic spinal cord injury who developed HO were identified through a database and assessed for signs/symptoms of HO at different time points in time following discharge. Findings showed that patients with complete spinal cord lesions had greatest risk for HO development. The presence of spasticity, thoracic trauma, pneumonia, and nicotine use increased risk for development. There was no correlation between age, sex, race, or length of hospital stay.6

B. Assessment

I. Signs and Symptoms
   a. Warmth, swelling, and erythema over a joint
   b. Fever. A recent report details iatrogenic fever being the only sign. Often, fever is seen in the presence of other inflammatory markers that can often mimic infection.6,11
   c. Gradual decrease in joint mobility

II. Rule out other causes of symptoms
   a. Vascular System
      i. Deep Vein Thrombosis
   b. Infectious
      i. Cellulitis
      ii. Osteomyelitis
   c. Oncologic
      i. Osteosarcoma
      ii. Osteochondroma

C. Diagnosis

I. Imaging
   a. Bone scan is the gold standard for diagnosis of HO as it shows findings earlier than radiographs.
   b. The early stage of HO maturation consists of immature bone not yet detectable by radiographs.17
   c. Recent research shows MRI may show changes consistent with HO early after onset of symptoms.
   d. 3D CT scanning1 offers a more accurate approach for guiding surgical excision of HO. Patients found to have significant HO of the hip following SCI or TBI were scanned and classified based on location; anterior, medial, lateral, posterior, and mixed. Use of 3D imaging was more accurate than classifying NHO based on radiologic findings. Other benefits include proper assessment of neurovascular structures, easier
excision in cases of incomplete HO, and decreased risk of iatrogenic injury.
e. Recent studies suggest ultrasound may be more specific in differentiating HO from other traumatic, inflammatory, or degenerative diseases of skeleton than bone scan. It has been shown to detect earlier than traditional radiographic studies and like 3D CT, can be used to visualize HO prior to surgical excision. It can also reasonably be used to follow maturation of HO as documented in prior studies. However, more research is needed to compare this to standard diagnostic measures.

II. Laboratory Data
a. Alkaline phosphatase levels can rise around first 2 weeks of injury in patients who develop HO and may return to baseline values at approximately 10-12 weeks.
b. Although it is nonspecific for osteogenic activity, this inexpensive test may be useful adjunct in diagnosis of early HO.
c. Elevated prostaglandin 24-hour urinary excretion in patients with suspicious symptoms may be helpful when determining need for bone scan.
d. Although nonspecific, Creatinine Kinase (CK) is typically higher in HO SCI patients and often suggests more involvement of surrounding muscle.
e. C-Reactive Protein correlates better with inflammatory activity of HO after SCI than does ESR. ESR was found to remain elevated even when clinical signs and symptoms weren’t present.

II. Management and Treatment Recommendations
A. Management and Treatment Recommendations.
   I. Recognition of signs, symptoms, and risk factors.
   II. Physical examination of joint and interpretation of available imaging and lab values.
   III. Obtain appropriate imaging study. Bone scan should be first line.
      a. If initial bone scan is negative but clinical findings are highly suggestive of HO, can start NSAIDs such as Indomethacin to down regulate prostaglandins thought responsible for cell differentiation into new bone formation.
      b. Banovac, et al studied the prophylactic effect of three weeks of indomethacin vs three weeks of placebo in SCI patients. There was a significantly lower incidence of HO in treatment group vs placebo, and those in treatment group developed HO significantly later than placebo.
      c. The most notable referenced study examined different in treatment outcome with Etidronate between groups with positive bone scan and negative radiographic findings vs. positive for both imaging modalities.
      d. Results suggested clinically significant HO can be prevented if treatment started before HO visible on radiographs. Ultimately, no significant difference was found between the two groups in development of HO.
e. Etidronate was most effective if initiated before radiographic evidence is seen.2,3

f. Radiotherapy can be used as primary or secondary prevention, either in conjunction with surgical excision or prophylactically in patients with severe injuries in whom HO development is high.12,17

g. Surgical excision is done to improve mobility and function, typically only performed if HO interferes with self-care, sitting in wheelchair, contributes to development of pressure ulcers, or causes compression of nerves and blood vessels.17 Previous studies suggested waiting for maturation of heterotopic bone prior to excision. However, recent studies suggested there is no relationship between surgical intervention relative to onset and risk of recurrence.

h. Therefore, NHO excision should occur when it begins to be troublesome, as soon as comorbid factors are under control, and the HO is sufficiently constituted for excision.10

III. Prevention and Education

A. Potential complications
   I. If HO not addressed and managed in a timely manner, loss of joint mobility, range of motion for ADLs and mobility can result.
      a. Peripheral nerve entrapment
      b. Decreased ROM progressing to ankylosis
      c. If HO overlies bony prominence, this directly predisposes to pressure ulcer/skin breakdown.12,17

B. Prevention
   I. Prophylaxis.
      a. Evidence shows that early treatment with NSAIDs early after SCI reduce the incidence of HO.
      b. Warfarin may be beneficial if administered after SCI. More studies are likely needed to validate this conclusion.
      c. Initiation of bisphosphonates such as Etidronate is most effective if initiated early. However, long term use in patients with concomitant bone injuries may impair fracture healing.
      d. Radiotherapy is thought to halt progression of HO by irradiating mesenchymal pleuripotential cells. Studies show when used as secondary prevention, it may improve joint range of motion and help prevent recurrence.18

C. Education
   I. After diagnosis is confirmed, completion of prescribed medication is recommended for resolution of HO.
   II. Close follow-up with physician is key in management of this condition and prevention of recurrence.
This guideline was developed to improve health care access in Arkansas and to aid health care providers in making decisions about appropriate patient care. The needs of the individual patient, resources available, and limitations unique to the institution or type of practice may warrant variations.

Guideline Developers
Guideline developed by Amanda Price, MD, in collaboration with the TRIUMPH team led by Thomas S. Kiser, MD, and Rani H Lindberg, MD.

Selected References


