

Nonhereditary Heterotopic Ossification

Implications for Injury, Arthropathy, and Aging

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Abstract

Nonhereditary heterotopic ossification (NHHO) usually arises in the setting of trauma, certain arthropathies, or following injury, often in the setting of common age-related conditions. In this article, we discuss the pathophysiology, diagnosis, and clinical findings in periarticular NHHO and the relevance to age-related pathology, as well as the prevention and treatment of NHHO. Except for the precipitating events or clinical conditions in which NHHO occurs, primary etiological mechanisms remain unknown. Many forms of NHHO develop in the context of injury and inflammation, suggesting that the formation of extraskeletal bone may share similar initiating events with ectopic ossification in fibrodysplasia ossificans progressiva.

Key Words: Heterotopic ossification; injury; arthropathy; aging.

Introduction and Definition of Terms

In postnatal life, new bone formation is normally restricted to regeneration of osseous tissue at sites of fracture. However, heterotopic ossification (HO), or the formation of bone outside the normal skeleton, can occur in soft tissue and is usually found within muscular, adipose, or nonmuscle fibrous/connective tissue. Ectopic bone formation is the only example of complete recapitulation of an organ system, replete with hard tissue, vascular, and marrow elements. Genetic forms of HO, such as fibrodysplasia ossificans progressiva (FOP) and progressive osseous heteroplasia, can be progressive soon after birth and throughout life. In contrast, nonhereditary heterotopic ossification (NHHO) tends to be limited and usually arises in the context of trauma, certain

arthropathies, or following injury that is often sustained in the context of age-related pathology.

Here the descriptors *heterotopic* and *ectopic* are used interchangeably to denote any extraskeletal ossification and HO is used as the term to describe *all* forms of extraskeletal bone formation, regardless of location. Related designations, such as myositis ossificans and osteoma cutis, refer to HO that evolves in muscle and skin, respectively. Neurogenic HO is the term used to describe extraskeletal bone formation secondary to central nervous system (CNS) injury.

A general classification scheme for NHHO based on the clinical setting is outlined in Table 1. As mentioned previously, NHHO occurs in the broad settings of injury, arthropathy, and aging, although these categories are not mutually exclusive. CNS, musculoskeletal, cutaneous, and vascular injury predisposes an individual to ectopic bone formation, and NHHO occurs as a clinically severe complications in as many as 19% of all individuals following major hip surgery, and in as many as 11% of those

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Table 1
Clinical Settings for Nonhereditary Forms
of Heterotopic Ossification

Injury
Traumatic head injury
Cerebrovascular accident
Paraplegia/quadruplegia
Poliomyelitis
Guillain-Barré syndrome
Muscle hematoma
Joint dislocation
Post-hip and knee arthroplasty
Surgical scars
Severe burns
Secondary osteoma cutis ^a
Atherosclerosis
Valvular heart disease
Arthropathy
Ankylosing spondylitis
Psoriatic arthritis
Seronegative arthropathies
Diffuse idiopathic skeletal hyperostosis
Aging
Post-arthroplasty
Atherosclerosis
Cerebrovascular accident
Valvular heart disease
Atherosclerosis
Miliary osteoma (of the face) ^b
Pressure ulcers ^{c,d}
Urinary tract infections ^d

^aPrimary osteoma cutis likely represents a hereditary form of heterotopic ossification and may overlap with or, in fact, be progressive osseous heteroplasia. The secondary form occurs in injured skin.

^bOccurs predominantly in middle-aged and older females.

^cAt the site of reactive soft-tissue ossification.

^dMay be a predisposing factor or a secondary complication of nonhereditary heterotopic ossification.

following traumatic brain injury (1,2). Bone formation limited to ligaments may occur with seronegative spondyloarthropathies or diffuse idiopathic skeletal hyperostosis. NHHO may be found in many age-related conditions, particularly in the context of common vascular pathology, as well as after total hip arthroplasty for age-onset degenerative joint disease. End-stage calcific valvular heart disease is prevalent in advanced age, and HO occurs in up to 13% of patients with this diagnosis (3). Age-related HO can

occur in a variety of other conditions associated with immobilization (e.g., neuromuscular disorders) or in the context of clinical factors common in the geriatric population, such as pressure sores, urinary tract infection, or trauma. Pulmonary ossification is much less common but can occur with chronic medical problems often found in older individuals, including left ventricular failure and secondary hyperparathyroidism (4).

Pathophysiology

NHHO lesions mature from the outside in, with the center of lesions likely consisting of undifferentiated mesenchymal or osteoprogenitor cells (5), whose origin may be local (i.e., resident in affected tissues) or remote, perhaps from bone marrow. Histologically or radiographically, complete bone maturation is usually completed in 6 to 18 mo. The histopathology of NHHO is largely unknown, with the exception of bone formation in end-stage valvular heart disease occurring through an endochondral process (3). Likewise, the osteoprogenitor cells responsible for NHHO are, as yet, uncharacterized. The origin of bone cells in ossified cardiac valves may involve aortic valve myofibroblasts or vascular smooth muscle cells (6,7), but whether these putative precursor cells are always resident in affected tissue or are derived from circulating osteoblast-like precursors that become resident after they enter the valve in response to endothelial injury, is unclear. These possibilities are not mutually exclusive.

Osteoinduction of receptive precursor cells may be mediated by humoral, neural, and/or local factors. Osteoblast-stimulating factors are variably present in the sera of patients with neurogenic HO (8,9), but may not play a direct role in bone induction (10). It seems likely that members of the bone morphogenetic protein (BMP) family, their associated pathways, and/or their antagonists, play a role in NHHO. Although BMPs can induce bone locally (11), no such factors have been directly implicated in NHHO. However, a mouse model of BMP4-expression targeted by the neural specific enolase promoter produces a progressive form of HO (12). Also, Glaser et al. have shown that BMP4 can induce ectopic bone locally that histologically recapitulates the stages of lesion formation seen in FOP (13). In both cases, the BMP antagonist noggin was able to prevent HO

when upregulated in each system. Neuron-derived factors may be involved in osteoinduction because they are a potential source of BMP antagonists and, at least in cases of neurogenic HO, CNS injury is intimately linked with predisposition to HO.

Local factors, released as the result of tissue injury and inflammation, may predispose an individual to NHHO by providing a permissive environment for ectopic bone formation. Possibilities include prostaglandin (PG) E₂ (14,15), BMP4 (13), and stromal cell-derived factor (SDF)-1 (16). PGE₂, an inflammatory mediator, enhances osteoblast differentiation in vitro, and its urinary excretion increases with early lesion formation in NHHO. BMP4 can induce HO when injected subcutaneously into rodents, and is also a chemoattractant for circulating mononuclear cells. SDF-1 has recently been invoked as a mediator of lesion formation in a mouse model of pulmonary fibrosis where, secondary to hypoxia-induced tissue injury, SDF-1 signals circulating mononuclear cells called fibrocytes to home to regions that eventually become fibrotic (17). This is noteworthy because pulmonary fibrosis is a pathological entity where NHHO is known to occur, and circulating fibrocytes have been implicated in FOP patients with active flares (18).

Many clinical factors may also contribute to a permissive environment for NHHO. As described later, these include pressure ulcers, urinary tract infections (UTIs), deep venous thrombosis, severe spasticity, and microtrauma to soft tissue and vascular components. Although these risk factors may provide the setting for HO by themselves, they may be secondary to sustained neurological or other injury.

Studies that have sought to establish a genetic predisposition to NHHO have failed to find any association with human leukocyte antigen or other markers. Except for the precipitating events or clinical settings in which NHHO occurs (*see* Table 1), primary gene defects, skeletal morphogens or antagonists, receptors, and target cells remain unknown.

Diagnosis and Clinical Findings in Periarticular NHHO

Clinically, symptoms of periarticular NHHO are nonspecific and manifest as pain, soft-tissue swelling, and periarticular stiffness (19). Signs are also nonspecific and may include erythema, warmth,

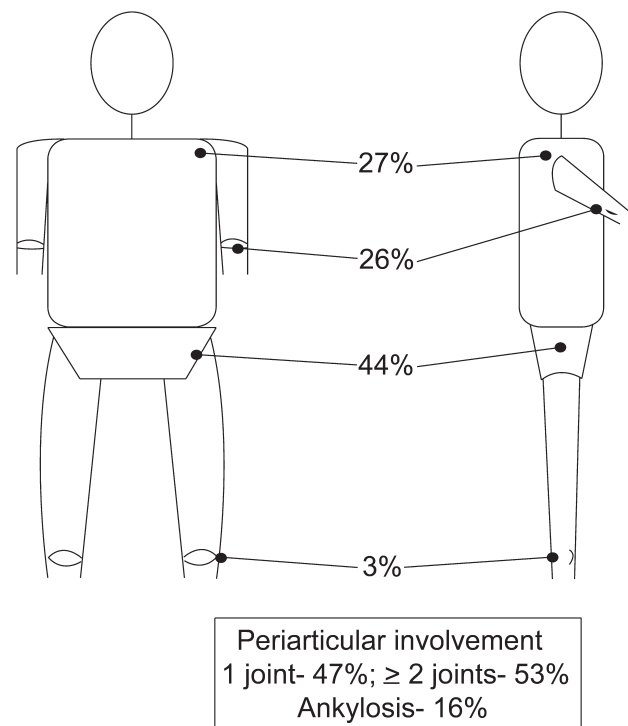


Fig. 1. Periarticular involvement of nonhereditary heterotopic ossification after traumatic brain injury. (Based on ref. 2.)

induration, and tenderness, with progressive decreased range of motion and possible ankylosis as later findings (19). Although complete bone maturation may take at least 6 mo, late signs and symptoms usually occur by 12 wk. Serum alkaline phosphatase is elevated early in lesion formation, plateaus by 8 wk, and declines afterward. Radionuclide bone scanning shows positive uptake during early vascular and late bone phases. Radiographic findings may reveal early osteogenesis by 5 to 8 wk post-lesion formation, and ultrasonography may be useful to differentiate early HO from a deep vein thrombosis (DVT).

Periarticular involvement in the setting of neurological NHHO tends to be located in paretic limbs, especially those with increased spasticity, and is more commonly found near proximal vs distal joints. Figure 1 shows the location and frequency of HO after traumatic brain injury. In this setting, periarticular involvement of two or more joints is about as likely as involvement near a single joint (2).

Complications of NHHO may include ankylosis, nerve entrapment, peripheral neuropathy, chronic

nerve ischemia, and complex regional pain syndrome I (formerly reflex sympathetic dystrophy). Decreased range of motion can limit flexion and extension, causing soft-tissue contractures and impairments in activities of daily living. Other consequences of a prolonged decrease in range of motion include pressure ulcers and disuse osteoporosis that may cause pathological fractures during lifting or positioning of a patient.

Implications for an Aging Population

Older individuals are at a potentially higher risk for NHHO owing to their predisposition to medical conditions and circumstances in which ectopic bone formation commonly occurs (*see* Table 1), as well as their increased likelihood of having risk factors for the development of HO. These risk factors include immobility and infection, as well as greater focal tissue injury and hematoma formation after trauma. In addition, the elderly have a greater vulnerability to complications of NHHO, potentially leading to further functional disability.

Arthroplasty

Heterotopic bone formation is well established as a frequent complication of total hip arthroplasty for age-onset degenerative joint disease, and even mild-to-moderate HO can cause postoperative symptomatology and adversely influence outcomes (20). The chance that patients undergoing primary hip replacement will develop HO is increased by the presence hypertrophic osteoarthritis or posttraumatic osteoarthritis characterized by hypertrophic osteophytosis, contralateral total hip replacement, trochanteric osteotomy, lateral or anterolateral surgical approach, previous hip surgery, subtrochanteric femoral osteotomy, or male gender. A combination of any of these factors, as is common in the older patient, results in a greater risk of developing HO. Increasing evidence suggests that HO occurs frequently after total knee arthroplasty, and that the incidence may increase following revision (21). HO has also been seen after shoulder arthroplasty.

Atherosclerosis and Valvular Heart Disease

Atherosclerosis almost universally affects the current aged population. Ossification of atherosclerotic plaques can occur during advanced differentiation of

fibrous plaques in a process similar to new bone formation. Degenerative calcification (with ectopic bone formation in up to 13% of calcified valves) has become the most common cause of aortic valve stenosis in industrialized countries, owing to the decline in rheumatic heart disease and increased longevity. End-stage aortic valve disease can demonstrate mature bone, fracture repair, and even bone remodeling (3). The severely calcified aortic valves in which bone can arise also display lesions that resemble atherosclerosis (22). Early etiological mechanisms shared by these two vascular pathologies include tissue injury and subsequent inflammation, factors also associated with initiation and progression of FOP bony lesion formation.

Pressure Ulcers, UTIs, and DVT

Some conditions that frequently occur in the geriatric population, such as pressure ulcers and UTIs, are less clearly and causally associated with NHHO. For example, the development of HO may precipitate these disease processes in the elderly, or HO may occur as the result of these processes. The same uncertainty is also true of DVT, which is also much more common with advancing age and is also associated with NHHO. A common etiological thread that links these entities with HO is immobilization. For example, prolonged stays in the intensive care setting (where pressure ulcers, UTIs, and DVTs can easily develop) are strongly associated with the occurrence of HO (23).

Prevention and Treatment

A standard conservative approach to the prevention of HO following total hip replacement is the postoperative use of nonsteroidal anti-inflammatory drugs (NSAIDs) (24). NSAIDs are thought to work by lowering levels of PGs that serve as powerful co-stimulatory molecules with BMPs in the induction of HO. Indomethacin and naproxen appear to be efficacious at reducing the incidence of HO after total hip arthroplasty. Other NSAIDs, including ibuprofen, flurbiprofen, diclofenac, aspirin, and naproxen, may also be effective in preventing the development of HO, but the agent, duration, and dosages have varied widely from study to study (24). Postoperative treatment with NSAIDs, before becoming standard of care, must be weighed against gastrointestinal and

renal complications, especially in the older patient, as well as the theoretical risk of delayed fracture healing.

Sodium etidronate inhibits bone matrix mineralization and possibly ossification at high doses. It has been used with some success in patients with neurogenic HO secondary to spinal cord injury (25). However, clinical use may be limited at high doses for sustained periods of time because of osteomalacia and impairment of normal ossification.

Perioperative radiotherapy is also effective at preventing HO after total joint arthroplasty (26). A second radiation treatment may be administered without acute or chronic complications (27). The success of using radiation therapy may be related to the reduction or elimination of mesenchymal stem cells, osteoprogenitor cells, and/or cells that may signal circulating osteogenic precursors to home to local tissue sites within the surgical field. Passive mobilization of an affected joint may be useful to prevent soft-tissue contractures and maintain or improve motion by introducing microfractures in the ectopic bone or producing a pseudoarthrosis of the ankylosed joint.

Surgical excision is the most widely used treatment in severe cases of periarticular HO. Indications for surgery include loss of motion, nerve compression, pressure sores, sinus tract formation, and abscess formation. Surgical excision of HO is aimed at increasing the range of motion of the involved joint. The optimal timing of the procedure is often disputed. For example, after brain injury, some studies recommend delay of surgery 12 to 18 mo to allow the bone to mature and reduce risk of recurrence (28). Others recommend delaying only until the neurological status of the patient is stabilized. The optimal method to prevent recurrence after surgical excision is programmed rehabilitation with appropriate physical therapy and pharmacotherapy.

The only effective treatment for severe ossific aortic stenosis is surgical replacement of the aortic valve. Guidelines for surgical intervention have been proposed (29).

Summary and Conclusions

NHHO usually arises secondary to trauma, some arthropathies, or with injury in the setting of common

age-onset conditions. Except for the precipitating events or clinical conditions in which NHHO occurs, primary etiological mechanisms remain unknown. Many forms of NHHO develop in the context of injury and inflammation, suggesting that the formation of extraskeletal bone may share similar initiating events with ectopic ossification in FOP. NSAIDs and local radiotherapy are currently the most effective treatment modalities for periarticular NHHO. Surgery is reserved for severe NHHO in all its forms.

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