Heterotopic ossification is the formation of bone in non-skeletal tissue, usually occurring in soft tissues surrounding joints. It can occur following local soft tissue or bone injury, in association with tumors, or in the vicinity of spastic or paralytic joints following central nervous system (CNS) injury or disease. When associated with CNS injury, it is termed neurogenic heterotopic ossification, occurring more commonly in patients with traumatic brain injury and spinal cord injury than in patients with stroke (and, interestingly, usually does not occur in patients with cerebral palsy or in children with anoxic brain injury). Heterotopic ossification was appreciated in the vicinity of joints of spinal cord injury patients as early as 1918, and in the following decades its connection with spinal cord injury and other CNS injuries became well established. More recently, it has been noted to develop in patients following tumors of the spinal cord or brain, as well as in those with CNS infections, such as cerebral abscess, encephalitis, or meningitis. Because the deposited bone in neurogenic heterotopic ossification usually occurs near or around joints, it is sometimes termed periarticular ossification.

No known etiology for the formation of neurogenic heterotopic ossification has been identified. Its relationship to CNS injury remains unknown. Heterotopic ossification does not seem to be a response or result of local soft tissue trauma or joint injury, since uninjured joints spontaneously form heterotopic ossification. The bone usually forms near major synovial joints, but has a predilection for joints surrounded by spastic muscles, especially in the hip, elbow, shoulder, and knee (Figs 1A-C).

Heterotopic ossification should be distinguished from myositis ossificans and other disorders that cause calcium deposition within the soft tissues. Myositis ossificans is the formation of bone within muscle (usually secondary to trauma), whereas heterotopic ossification usually forms between muscle planes. In disorders such as a tumoral calcinosis, secondary hyperparathyroidism, hypervitaminosis D, gout and pseudogout, para-articular chondroma, and calcinosis circumscripta, the calcium deposition may occur within soft tissues. Radiographs in these afflictions causing calcium deposition can usually be distinguished from heterotopic ossification by their deposition of amorphous calcified opacities, rather than mature bone.
The presence and severity of neurogenic heterotopic ossification seem to be associated with severity of spasticity.\textsuperscript{22,25,31,32,41,42} Spastic patients with brain injury and spinal cord injury are at increased risk for developing heterotopic ossification. Heterotopic ossification in spinal cord injury patients occurs more often in spastic limbs than in flaccid limbs. In acquired hemiplegia from brain injury, the heterotopic ossification develops on the hemplegic (spastic) side. Patients with massive heterotopic ossification production usually have severe spasticity, and also have the highest recurrence rate after heterotopic ossification resection.\textsuperscript{4,25,31,42} Joint trauma or surgical stabilization of fractures in a patient with CNS disease increases the occurrence of heterotopic ossification.\textsuperscript{4,25,31} In addition, pressure sores in the vicinity of a proximal joint seem to be associated with an increased incidence of heterotopic ossification.\textsuperscript{31,32}

There may be evidence suggesting a genetic predisposition for neurogenic heterotopic ossification based on other types of heterotopic ossification (ie, hereditary disorders such as fibrodysplasia ossificans progressive).\textsuperscript{31} Initial studies suggested a possible association with the human leukocyte antigens (HLAs),\textsuperscript{33,31,43} but follow-up investigations seem to have failed to confirm these findings.\textsuperscript{28}

**INCIDENCE AND JOINTS INVOLVED**

The reported incidence of neurogenic heterotopic ossification in patients with traumatic brain injuries varies from 11\% to 75\%. Loss of motion occurs in about one third of patients, and complete ankylosis develops in about 10\% to 16\%.\textsuperscript{30,31,41,42} Heterotopic ossification is more common in traumatic brain injury and spinal cord injury patients than in stroke patients, and usually forms in the neurologically impaired limbs. Both spastic or flaccid extremities may be affected, although spastic limbs are involved more often.\textsuperscript{22,31} Variable amounts of bone can be formed, from minimal bone deposits without clinical significance, to large, bulky, tumor-like masses of palpable bone that restrict motion or lead to joint ankylosis. The bone is usually deposited between the muscle planes; it is not usually formed within muscles or within joints. The bone can, however, distort or displace neighboring muscles or neurovascular structures. Ossification may completely encase or surround neurovascular bundles.

In traumatic brain injury and spinal cord injury, the hip is the most common joint affected, followed by the elbow, shoulder, and, less commonly, the knee. In spinal cord injury, the hip is most commonly affected, followed by the knee, elbow, and shoulder (Fig 1).\textsuperscript{31} In both brain injury and spinal cord injury, peripheral joints such as the wrists, ankles, hands, and feet are virtually never involved.\textsuperscript{31}

At the hip, ossification in brain-injured patients usually occurs inferomedially to the joint, and is usually associated with adductor spasticity (Fig 2). The bone mass may develop anteriorly or posteriorly, or appear diffuse. Concomitant trauma to the hip in the setting of a brain injury appears to increase heterotopic ossification formation. The bone mass may encase the femoral artery and vessels anteriorly or the sciatic nerve posteriorly.

At the elbow, the site of heterotopic ossification production is variable, originating either anterior if flexor spasticity is present or posterior to the joint if extensor tone is present. Anteriorly, the bone is usually deposit-
ed deep to the brachialis but superficial to the joint capsule. Posteriorly, the bone is usually located between the triceps and the joint capsule. Medial and lateral locations are also common, and the bone may develop adjacent to the collateral ligaments (Fig 1C). Tardy ulnar nerve palsy can occur from direct heterotopic ossification compression or secondarily from joint ankylosis in a position of elbow flexion.

Shoulder involvement is usually associated with spasticity of the internal rotator muscles. Although varying amounts of bone may be formed, ankylosis is rare. Even with a large amount of bone, motion is usually maintained through formation of a pseudoarthrosis.

Knee involvement is more common in spinal cord injury patients than in patients with traumatic brain injury. The medial or anteromedial areas are the usual sites of involvement (Fig 3). Loss of motion occurs to varying degrees. The relatively superficial location of the formed bone can lead to a tender, palpable exostosis.

**TIME OF DEVELOPMENT**

The time of initial occurrence of heterotopic ossification is variable. Detection is usually at about 2 months post-neurologic injury, but can range from 2 weeks to 12 months post-injury. Once diagnosed, time to maturation is even more variable and often difficult to assess. "Maturation" generally refers to the time of cessation of bone growth, and is usually based on radiographic appearance (discussed below), stabilization of levels of serum alkaline phosphatase levels (which may not always be reliable), and decreasing or static activity on repeated technetium bone scans and sulfur colloid scans. The bone usually increases in size over a 6-month period and shows progressive signs of maturation thereafter.

**CLINICAL FINDINGS AND ASSOCIATED PROBLEMS**

An inflammatory response typically precedes or coincides with formation of heterotopic ossification. Clinical findings during bone deposition include tenderness, warmth, swelling, erythema, and stiffness of the involved joint. These findings may mimic infection, thrombophlebitis, or tumor. Occasionally a firm or hard mass is palpable. Once mature, the swelling, warmth, and erythema may subside, leaving a variable amount of joint stiffness and sometimes a palpable mass.

If the deposition of heterotopic ossification results in mechanical restriction of joint motion, secondary soft tissue contractions may form involving surrounding skin, muscles, ligaments, and neurovascular bundles. Discomfort is often present when limb sensibility is intact. Loss of motion impairs function, and may prevent sitting, transfers, dressing, and hygiene. Restricted positioning secondarily risks development of pressure sores and subsequent infection. Chronic joint flexion or direct pressure on peripheral nerves, especially at the elbow, may cause chronic nerve ischemia and compression, resulting in peripheral neuropathy. Lack of joint motion increases the likelihood of pathologic fracture of the osteoporotic bone during patient positioning or lifting.

Fig 2. AP radiograph of hip in brain-injured patient showing mass of bone located inferomedially.

Fig 3. AP (A), lateral (B), and Merchant axial radiograph (C) of knee showing heterotopic ossification. Note the bone mass located anteromedially.
Although initial radiographs may not detect early heterotopic ossification, the technetium bone scan will usually be positive, demonstrating increased metabolic bone activity within 2 to 4 weeks of injury (often positive up to 4 weeks before heterotopic ossification is observed radiographically). The three-phase bone scan appears to be the best method for early detection of heterotopic ossification, using labeled methylène diphosphonate. The activity of the bone scan may remain fully active during the first year, and continue to show various levels of uptake for many months or even years.

Radiographically, heterotopic ossification development has been divided into three stages: early, intermediate, and mature. The early stage indicates increased activity on bone scan but no radiologic findings. The intermediate stage indicates radiographically appearing bone that is not mature. The mature stage indicates well-developed, mature-appearing bone.

Computerized tomography (CT) scanning is helpful for more clearly defining the margins of the heterotopic ossification mass in three dimensions. This is specifically helpful in preoperative planning for resection, especially in the hip and elbow regions to establish the relationships of the bone to muscle and neurovascular structures.

During active bone formation of heterotopic ossification, serum alkaline phosphatase is usually elevated. It usually begins to increase at about 2 weeks post-neurologic insult, and may remain persistency high for months or years, reaching elevations as high as 500 IU. The alkaline phosphatase level does not always correlate with heterotopic ossification peak activity, inactivity, or number of heterotopic ossification lesions. Though non-specific, the alkaline phosphatase levels may still constitute one of the earliest, most convenient, and least expensive laboratory tests for heterotopic ossification evaluation. Co-existing fractures must be excluded, as these will also elevate the serum alkaline phosphatase.

**Histologic Findings**

Initial studies have indicated that the formation of neurogenic heterotopic ossification histologically resembles that of woven bone, with areas of concurrent inflammation. Early in the development (within the first 8 months), it usually appears as disorganized lamellar bone with osteoblastic activity and hypervascularity. Eventually, the bone develops into mature cortical bone, with a decrease in osteoblastic activity, decrease in hypervascularity, and a more organized lamellar pattern. It may take 18 months before the bone appears histologically as mature bone.

More recently, Haider et al. studied the microscopic development of heterotopic ossification in brain-injured patients more in-depth. In the early stage (with increased activity on bone
scan but no radiologic findings), histologic findings under light microscopy have shown fibrofatty tissue and fibromuscular tissue with no evidence of calcification or bone formation. Electron microscopy has demonstrated bundles of collagen fibers in an organized arrangement. Along these collagen fibers, deposits of calcification and few fibroblasts are present. In the more advanced stages of heterotopic ossification, larger aggregates of calcific deposits, inflammatory cells, and osteoblasts have been noted along with islands of bone. Collagen fibers are present but demonstrate a more random orientation. In all stages of heterotopic ossification, no cartilage cells were observed in the isolated tissues. These findings confirm that heterotopic ossification in brain-injured patients is a process similar to intra-membranous ossification rather than enchondral ossification. It does not involve cartilage formation as an intermediate stage, but rather a direct calcification and ossification of the collagen matrix.

**Management**

Non-surgical management of symptomatic heterotopic ossification includes treatment of associated pain, maintenance of joint motion using a comprehensive physical and occupational therapy program, medications to decrease inflammation and inhibit bone production, and/or prophylactic low-dose radiation. If non-surgical methods are not adequate and loss of motion or ankylosis develops, surgical resection of bone (with possible release of associated soft tissue contractures) can be undertaken. Use of radiation as an adjuvant for neurogenic heterotopic ossification, either preoperatively or postoperatively, is under investigation but has shown to be encouraging for treatment of other types of heterotopic ossification (such as posttraumatic and post-arthroplasty heterotopic ossification).

**Mobilization.** Maintenance of motion by passive mobilization comprises an effective but controversial method of treatment for neurogenic heterotopic ossification. Concern has been raised that joint manipulation may increase the inflammatory response, which in turn increases the heterotopic ossification production. Supporters of this theory feel that experimental heterotopic ossification has been convincingly produced using forceful manipulation of joints in an animal model. Critics of these studies, however, point out that these models probably represent a form of traumatic heterotopic ossification, produced by joint injury. Evidence for the detrimental effects of manipulation in neurogenic heterotopic ossification still seems to be lacking. Conversely, the beneficial effects of joint mobilization in heterotopic ossification have been demonstrated in clinical trials, and have become an accepted method of treatment. Though mobilization may not alter the formation of bone, it can prevent secondary soft tissue contractures and maintain or increase motion by producing microfractures or pseudoarthrosis through an ankylosing mass. Aggressive passive motion does not seem to aggravate the inflammatory response or adversely affect bone production. In a patient with intact sensibility, mobilization may be difficult because of associated discomfort, and analgesics and anti-inflammatory medications are helpful. Mobilization is also difficult because of the co-existing spasticity. Despite the difficulty of performing passive or active limb mobilization in these patients, attempts at maintaining motion (along with splinting used to maintain proper position) should be continued, because secondary soft tissue fixed contractures will develop if the joint motion is not maintained. Forceful manipulation of the joint under anesthesia is also controversial, but has been proven beneficial and effective to gain motion in some patients. All manipulations must be done with caution to prevent pathologic fracture of osteoporotic long bones.

**Antinflammatory medications.** Antiinflammatory medications are useful for patient comfort in the early or intermediate stages of bone formation when an inflammatory process may coexist. Indomethacin, ibuprofen, and aspirin are thought to also inhibit bone production during heterotopic ossification formation by inhibiting prostaglandin synthetase. Indomethacin has been shown to be effective in clinical studies in the prophylactic prevention of heterotopic ossification formation after total hip replacement. However, the effectiveness of these non-steroidal antiinflammator medicatations to prevent neurogenic heterotopic ossification is not well established and warrants further investigation.

**Disodium etidronate.** Disodium etidronate has demonstrated promising results in preventing the occurrence of heterotopic ossification or in reducing its extensiveness once it is clinically evident. However, its long-term efficacy remains questionable. Disodium etidronate works by inhibition of the formation and growth of hydroxyapatite crystals. Recommended dose is 20 mg/kg/day for prophylaxis, initiated prior to clinical or radiographic evidence of heterotopic ossification and continued for 3 months. For established heterotopic ossification, treatment is initiated and continued for 6 months. Approximately 10% to 20% of patients will continue to exhibit formation of heterotopic ossification after 6 months of treatment. Prolonged treatment of high doses of disodium etidronate for longer that 6 months is not desirable because of side effects (ie, long bone fractures).

**Operative management.** Surgical resection of heterotopic ossification should be considered in refractory cases not satisfactorily relieved with conservative methods. Indications for resection include limitation of motion with function loss; joint immobility causing difficulty in patient positioning, sitting, dressing, transfers, or hygiene; ankylosed joints resulting in pressure sores or increasing the risk for skin breakdown, or heterotopic ossification.
contributing to or causing peripheral neuropathy (from either limb deformity or by direct nerve compression). Resection requires careful pre-operative planning, as surgery is associated with high morbidity from hemorrhage, sepsis, and re-ankylosis. The patients with severe neurologic disorders are often debilitated and are suboptimal surgical candidates. Neurovascular structures are at risk because anatomy is often distorted and nerves or vessels may be displaced or completely encased in the bone mass. Preoperative computerized axial tomography, standard polytomography, or magnetic resonance imaging help delineate the three-dimensional configuration of the bone mass and relationships to soft tissues (Fig 5). Cautious dissection, good visibility and hemostasis, neurovascular bundle isolation and protection, and adequate bone mass exposure are required. In resections involving large amounts of bone (especially in the hip), the exposed cancellous bone resection surfaces will often lead to continued postoperative blood loss. Although intraoperative hemostasis using bone wax, coagulation, and appropriate vessel ligation minimize bleeding, blood replacement is often necessary. Surgical drains are usually indicated, especially when dead space is created by removal of a large bone mass.

The timing of resection of heterotopic ossification is controversial. It is generally accepted that early resection of "immature" bone has a higher incidence of recurrence and hemorrhage than resection of mature bone. However, delaying surgery until bone is "mature" may take years and results in problems associated with prolonged joint immobilization (i.e., fixed soft tissue contracture, intraarticular adhesions, and cartilage erosions). Evaluation of bone maturity is difficult, and because parameters used are not consistently reliable, specific recommendations for time of resection of heterotopic bone have not been well established. In the past a minimum delay of 14 months following diagnosis has been recommended to allow adequate time to achieve bone maturity and thus minimize hemorrhage and chance of recurrence. However, a more aggressive approach, with earlier resections, minimizes associated joint and soft tissue problems. Resection requires only removal of adequate bone to acquire desired motion. The entire mass does not require resection to achieve motion, and often only a large wedge of bone needs removal.40-43

If concomitant soft tissue contractures exist, myotendinous lengthenings, recessions, or releases can be performed, depending on the preoperative functional status of the limb.44,45,59,60,66-68 Remaining soft tissue contractures will often respond to an aggressive mobilization therapy program once the heterotopic ossification is resected (and therefore soft tissue releases are not always warranted at the time of heterotopic ossification resection). Contracted neurovascular structures may be the limiting factor to the amount of joint deformity that can be corrected at the time of surgery.

Following resection, close follow up and continued therapy are required to maximize gains from surgery. Postoperative low-dose irradiation (500 to 700 rads X 1, or, alternatively, 1000 rads given in 200-250 rad increments over 4 or 5 consecutive days) and/or indomethacin prophylaxis can be considered to help prevent recurrence. Mobilization and corrective splinting should be reintroduced early to maintain motion. Secondary soft tissue contractures require gradual stretching to achieve maximum motion. Continued therapy for months may be necessary to maximize or maintain outcomes of surgery.

**CONCLUSION**

Neurogenic heterotopic ossification following central nervous injury is a process of bone formation near major joints occurring with unknown etiology. The hip, elbow, shoulder, and knee are most commonly affected. Loss of motion or complete ankylosis may develop, and can result in painful deformity, loss of function, problems with positioning, dressing and hygiene, peripheral neuropathy, and increased risk for pressure sore formation. Treatment includes management of associated spasticity and pain, maintenance of joint motion, the use of pharmacologic agents to decrease inflammation and bone production, and, when severe or refractory, surgical resection. Although surgical resection is associated with high morbidity, it remains an effective means of increasing motion and alleviating the many associated problems. Prolonged therapy and close clinical follow up are required to minimize recurrence. Despite the valuable contributions of many researchers and clinicians, many questions and controversies still remain concerning the etiology, prevention, and treatment of neurogenic heterotopic ossification.

**REFERENCES**


