Current concepts in the development of heterotopic ossification

Heterotopic ossification can be defined as the formation of bone in tissues which normally exhibit no properties of ossification. It is characterised by the rapid development of calcified bone in soft tissues. Ectopic bone can develop from immature osteoid in a matter of weeks.

The development of heterotopic ossification has been shown to be associated with many predisposing factors including neurological injury, both to the spinal cord and the brain, major joint surgery and burns.\(^1\)\(^2\) Marked variation can occur in the incidence and location of bone formed and in the resulting complications.

The first description of heterotopic ossification after neurological injury was by Dejerine and Ceiller\(^1\) who detailed the clinical, anatomical and histological features of ectopic bone formation in soldiers who sustained spinal injuries during the First World War. Heterotopic ossification after traumatic brain injury was first reported by Roberts\(^2\) who described involvement of the elbow in patients with cerebral injury and a prolonged period of coma.

The incidence following brain injury has been reported to vary between 11% and 22%.\(^3\)\(^4\) The most common joints to be affected are the hip, elbow and shoulder. After such injury an accelerated rate of fracture healing has also been reported with the formation of exuberant callus at fracture sites.\(^6\)\(^7\)

Since the original report of heterotopic ossification after traumatic brain injury,\(^2\) there have been a number of papers describing the incidence, location and management. This review provides an analysis of the papers on this topic published previously and discusses the aetiology, pathophysiology and the current concepts of treatment.

Heterotopic ossification

Aetiology. Although much has been written about heterotopic ossification it is clear that as yet there is no clearly defined mechanism for its occurrence. It has a multi-factorial aetiology with several risk factors identified which predispose to its formation. Trauma is a constant feature and in the case of head injury, traumatic damage to the brain. Other general factors have been identified from studies of patients undergoing total hip arthroplasty who have developed heterotopic ossification (Table I). It is uncertain whether these risk considerations play a significant role in patients with head injuries.

Specific factors have been implicated in the latter group of patients (Table II). Limb spasticity is associated with a greater risk of developing heterotopic ossification. Garland\(^5\) found when studying patients with traumatic brain injury that 89% of involved joints were in spastic limbs, with the hip joint being most commonly affected. Another related factor is the decorticate and decerebrate postures which may occur after such injury.\(^9\) The extent of brain damage has also been linked to the formation of heterotopic bone. Gennarelli\(^10\) suggested that diffuse axonal injury may predispose to the development of heterotopic ossification more than focal brain injury, as patients with the former injury tend to be younger, may have a period of coma and often develop limb spasticity. A long period of immobilisation is also associated with the formation of heterotopic ossification.\(^11\) It thus may occur after prolonged coma or the multiple long bone fractures which are often associated with a severe head injury.\(^6\)

Many patients who suffer a head injury require respiratory ventilation, sometimes to assist in the control of intra-cranial pressure. Ventilation is known to cause homeostatic changes of systemic alkalosis which result in the formation of heterotopic bone.\(^12\) The changes in pH associated with alkalosis can cause modification of the precipitation kinetics of calcium and phosphate. Studies of the effect of modifying the pH at fracture sites has shown that as the local environment goes from acidity to alkalinity more callus is deposited.\(^12\)

There may also be a yet unidentified genetic predisposition to the development of ossifica-
Heterotopic ossification occurs rarely in the knee following head injury. When present, the most common site is in the inferomedial aspect of the distal femur, but it can occur in any plane. In a study of 496 patients with head injury heterotopic ossification was seen in three planes, medially, laterally and posteriorly.\textsuperscript{13,14}

The location of heterotopic ossification after head injury.

Following head injury heterotopic bone tends to form in para-articular sites. The most commonly affected joint is the hip, then the shoulders, elbows and rarely the knee.\textsuperscript{13}

Bone tends to be deposited anterolaterally, inferomedially and posteriorly in contrast to after injury to the spinal cord when ossification tends to occur in the anteromedial plane.\textsuperscript{5,14}

The distribution of ossification around the elbow is similar to that around the shoulder. In the elbow, it occurs most commonly either anteriorly in the flexor muscles or posteriorly in the extensors. Of the joints affected by heterotopic ossification after head injury, ankylosis is most likely to occur in the elbow and it usually occurs posteriorly.\textsuperscript{13}

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Ankylosis of the knee is rare. However, the knee is the second most common site for the formation of heterotopic bone following a spinal cord injury.\textsuperscript{15}

Clinical features. The development of heterotopic ossification may be detected in a number of ways. Clinical examination may reveal a swollen, warm painful joint. This is often associated with a decreased range of movement and it can be difficult initially to differentiate from infection, as the patient often has an associated pyrexia.\textsuperscript{6,13,14}

Accelerated bone healing and heterotopic ossification after head injury. In the patient who has sustained a head injury and an associated fracture, there is often the clinical perception that fracture heals more rapidly. Clinical and radiological findings of accelerated bone healing and the formation of more callus have been reported.\textsuperscript{7,8}

There is no universal agreement about this concept since other studies have shown that fractures in these patients heal at the same rate and frequency as similar injuries in patients without a head injury.\textsuperscript{16-20} It has been proposed that the accelerated fracture healing observed after head injury is actually a variant of heterotopic ossification.\textsuperscript{16,21} Some histological evidence to support this is derived from the unusual pattern of callus formation seen in patients with head injuries.\textsuperscript{21} Such callus first matures peripherally whereas in normal fracture callus maturation initially occurs centrally. As yet the question of whether a head injury genuinely results in accelerated fracture healing rather than a form of heterotopic ossification occurring at the fracture site remains unanswered.

Biochemical changes. Biochemical changes may also be useful in making the diagnosis. The serum alkaline phosphatase level reflects osteoblastic activity and an increase has been demonstrated up to seven weeks before the clinical symptoms of heterotopic ossification become evident.\textsuperscript{19,22} However, it can be difficult to interpret the levels of serum alkaline phosphatase following injury if the patient has concomitant fractures or liver disease, as these conditions will also produce an increase in levels, but it is a minimally invasive, inexpensive screening tool to monitor the formation of heterotopic ossification.

Another useful biochemical assay in the assessment of the development of heterotopic ossification is the excretion of prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) in the urine. In a study of the 24-hour urinary excretion of PGE\textsubscript{2} after acute spinal cord injury, eight of 44 patients developed heterotopic ossification and an increase in the excretion of PGE\textsubscript{2}.\textsuperscript{15} The increase only continued until the ossification reached maturity. The 24-hour urinary excretion of PGE\textsubscript{2} can be a valuable indicator in the early diagnosis of heterotopic ossification.

Radiological changes. Plain radiographs can confirm the presence of heterotopic ossification although changes may not be evident during the initial phases. It may take up to six weeks for ossification to be evident on a radiograph and it is not generally a confirmatory investigation until more than two months after injury.\textsuperscript{14} However, radiographs are an inexpensive and simple method of assessing the extent of ossification.

For the early detection of ossification and assessment of its maturity, plain radiographs have been largely superseded by three-phase bone scintigraphy\textsuperscript{6,13,14,22} using \textsuperscript{99m}T-c-methylene disphosphonate. Flow studies and blood
The conditions and stimulating factors involved in the development of heterotopic ossification, but the mechanism for this is poorly understood. The conditions and stimulating factors involved and the possible interactions resulting in heterotopic ossification are illustrated in Figure 1.

**Mesenchymal stem cells.** The term mesenchymal refers to the developing loose connective tissue of an embryo, mainly derived from the mesoderm, which eventually gives rise to most of the cells in adult connective tissue. The definition is generally extended to include connective tissue cells in adult tissues such as fibroblasts and the cells that form bone, cartilage, fat, tendon, muscle and nerve tissue. Many mesenchymal tissues contain committed, lineage-directed mesenchymal precursor cells which participate in local regeneration, such as the satellite cell in skeletal muscle or the adipocyte progenitors of adipose tissue.

Mesenchymal stem cells or human bone marrow stromal stem cells are pluripotent progenitor cells with the ability to generate cartilage, bone, muscle, tendon, ligament and fat. These primitive progenitors exist postnatally and exhibit the characteristics of stem cells, namely a low incidence and an extensive potential for renewal. Mesenchymal stem cells can give rise to other types of mesenchymal tissues than the one they represent, and are thought to play a pivotal role in the development of heterotopic ossification.

**Stimulating agents.** Mesenchymal stem cells alone cannot produce heterotopic ossification. Stimulating agents are also required. It has been thought that bone morphogenetic proteins in the soft tissues may stimulate the development of heterotopic ossification. In a study almost 30 years ago by Urist et al., the effect of extracted non-collagenous proteins from bone matrix was assessed when cultured with vascularised and avascular muscle tissue. In the vascular system bone developed and in the avascular system cartilaginous tissue was formed. The conclusion was that a bone morphogenetic protein was the stimulating agent, and in the correct local environment this could cause the transition of mesenchymal stem cells to bone.

The addition of other stimulating factors such as interleukin-1β to bone morphogenetic proteins has been shown to further enhance bone formation. Growth hormone, prolactin, insulin-like growth factor type-I and basic fibroblast growth factor have all been implicated in the formation of heterotopic ossification after head injury. It would appear that a complex and as yet poorly understood interaction of a wide variety of stimulating factors is involved.

**Stimulating factors related to head injury.** Circulating factors which promote heterotopic ossification are thought to be present in patients after head injury. The serum from patients with head injuries has been shown to promote mitogenesis and cell division in a rat osteoblast cell culture model. It has been hypothesised that the circulating factors in these patients promote release of local stimulating factors which promote heterotopic ossification, although this specific interaction has not yet been shown.

**Local tissue environment.** Various factors in the local tissue environment have been implicated in the development of
heterotopic ossification. These include disturbances involving the microvasculature and changes in oxygen tension, pH and blood flow. Punch biopsies of skin and soft tissue in areas of heterotopic ossification in patients with injury to the spinal cord and paraplegia have shown alterations in the endothelial cells and basement membrane of capillaries and small vessels. The resulting microvascular changes in the skin and subcutaneous tissue led to the theory that vascular changes may induce hypoxaenic alterations in the para-articular soft tissues, leading to metabolic changes which may contribute to the development of heterotopic ossification.

Callus is deposited at fracture sites as the local pH changes from acid to alkaline, so enhancing the precipitation of bone salts such as calcium and phosphate. Mechanical respiratory ventilation may produce a systemic alkalosis which can also affect the local tissue environment. It is possible that the alkalosis seen in patients during prolonged respiratory ventilation may be a causative factor in the development of heterotopic ossification, which has been described in ventilated patients with acute respiratory distress syndrome after sustaining multiple injuries but no head injury.

**Treatment of heterotopic ossification**

The treatment of heterotopic ossification is largely dependant on the severity and extent of the ectopic bone and the amount of associated functional disability. Clinical examination allows a crude assessment of the long-term outcome and joint mobility. Patients with persistent spasticity and poor neurological recovery have a high incidence of recurrent ossification and poor joint mobility. Treatment may start with physiotherapy and joint mobilisation and pass through a spectrum of medical therapy, radiotherapy and surgical excision.

**Physiotherapy.** In the patient with heterotopic ossification, careful physiotherapy has been shown to be of benefit. This should involve assisted range of movement exercises with gentle stretch and terminal resistance training. Care should be taken not to move the joint beyond its pain-free range of movement as this can exacerbate the condition. Physiotherapy is often combined with other forms of treatment in order to provide maximum therapeutic benefit.

**Medical management.** Medical treatment aims to prevent the formation of heterotopic ossification following injury and to avoid recurrence after surgical excision.

The groups of drugs used in the medical management of heterotopic ossification include non-steroidal anti-inflammatory drugs (NSAIDs) and bisphosphonates. NSAIDs and in particular indomethacin, have been shown to be of benefit in preventing the formation of heterotopic bone after total hip arthroplasty. They have been helpful in preventing heterotopic ossification following injury to the spinal cord and after excision of ectopic bone in those with a head injury. However, some patients experience side-effects. Recent work has studied the efficacy of Cox-2 selective inhibitors, in particular meloxicam, compared to indomethacin in the prevention of heterotopic ossification after hip arthroplasty. Meloxicam has been shown to be a more expensive alternative, without reducing the incidence of ossification and it may cause it to increase.

Bisphosphonates, in particular etidronate, have also been used in the management of heterotopic ossification. One of the pharmacological effects of etidronate disodium is to block the aggregation, growth and mineralisation of calcium hydroxyapatite crystals. Despite extensive use in clinical practice, there has not been conclusive evidence to show that etidronate causes significant arrest of the development of heterotopic ossification.

**Radiotherapy.** Radiotherapy has been used successfully to prevent heterotopic ossification after arthroplasty of the hip. It is difficult to investigate its use in patients with ossification after head injury. The site of the ectopic bone after hip surgery is predictable, whereas that after head injury is difficult to forecast. Prophylactic radiotherapy, the only form shown to be of benefit in preventing heterotopic ossification, is thus difficult to administer in these patients. Radiotherapy has not been shown to be of benefit in reducing the volume of established ectopic bone but it may help in controlling pain refractory to indomethacin in patients with head injury.

**Surgical excision of heterotopic bone.** Surgical intervention is used either to alter the position of a joint or to improve its range of movement. Garland recommended timetables for the surgical removal of heterotopic ossification depending on the aetiology. He advised surgery after six months following traumatic heterotopic ossification, one year following spinal cord injury and 18 months after head injury. The long interval of 18 months is intended to ensure the maturity of the ectopic bone and reduce the likelihood of recurrence. Another factor in the timing of surgical intervention is the neurological condition of the patient. Patients with head injury commonly have some neurological impairment. Studies have shown that patients with more severe cognitive and physical impairment have poor results from surgery with a high rate of recurrence and that those with good neuromuscular control before operation have the best functional result. Continuous passive motion after surgery has been shown to be beneficial in improving the eventual range of movement and the administration of indomethacin is a useful adjunct to reduce the incidence of recurrent ossification.

Heterotopic ossification remains a poorly understood condition with little known of the exact mechanisms involved. Its development can be reduced by the judicious use of treatment regimes including physiotherapy, NSAIDs and occasionally radiotherapy. Excision may give good results but there is a significant risk of recurrence. The old adage is true in the management of heterotopic ossification, as in many other conditions 'prevention is better than cure'.

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References


