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REVIEW ARTICLE

HETEROTOPIC OSSIFICATION: A REVIEW

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Heterotopic ossification is defined as the presence of lamellar bone at locations where bone normally does not exist. The condition must be distinguished from metastatic calcifications, which mainly occur in hypercalcaemia, and dystrophic calcifications in tumours. It is a frequent complication following central nervous system disorders (brain injuries, tumours, encephalitis, spinal cord lesions), multiple injuries, hip surgery and burns. In addition to this acquired form, hereditary causes also exist, such as fibrodysplasia ossificans progressiva, progressive osseous heteroplasia and Albright's hereditary osteodystrophy. Although these conditions are extremely rare, they can provide useful information on the physiopathology of heterotopic ossification, and thus lead to novel and causal treatment modalities. Heterotopic ossification is no trivial complication. A limitation of the range of joint motion may have serious consequences for the daily functioning of people who are already severely incapacitated because of their original lesion. Increased contractures and spasticity, pressure ulcers and increasing pain further compromise the patient's capabilities. Consequently, we feel that attention should be paid to the pathogenesis and particularly the prevention and treatment of this disorder.

Key words: heterotopic ossification, myositis ossificans, bone morphogenic protein, etidronate.

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INTRODUCTION AND BACKGROUND

Heterotopic ossification (HO) was first described in 1692 by Patin in children with myositis ossificans progressiva (1). In 1883 and in 1918 a clearer description was provided by Riedel (2) and by Déjerine & Ceillier (3), respectively. During World War I, HO was predominantly observed in soldiers who had become paraplegic from intramedullary gunshot wounds. At that time the relationship between oedema and traumatic lesions of the nervous system was already established. In 1961, Damanski (4) related a lower incidence rate to more adequate treatment after trauma.

Based on a hypothetical etiopathogenetic mechanism several terms have been used to denote this condition, e.g. ectopic ossification, myositis ossificans, neurogenic ossifying fibromyopathy and paraosteoarthropathy or periarticular ossification. In the current medical literature the term heterotopic ossification is used.

DEFINITION

HO is defined as the formation of lamellar bone inside soft-tissue structures where bone normally does not exist. Myositis ossificans refers rather to a condition in which ectopic bone is formed within muscles and other soft tissues. Three types are distinguished: myositis ossificans circumscripta, myositis ossificans progressiva and localized traumatic myositis ossificans (5). Ectopic calcification is a mineralization of soft-tissue structures, which usually follows chemical or physical trauma, as in tendinitis calcarea. Histologically, a calcium deposit rather than new bone would be formed.

As yet, there is no consensus on the definition and classification of HO. The most widely used classification system is still that developed by Brooker et al. (6).

EPIDEMIOLOGY

The incidence of HO after total hip arthroplasty (THA) ranges between 16% and 53%, and is highest in predisposed patients (7). This wide divergence is dependent on the individual centres, population, study interval, method of data acquisition and duration of follow-up (8). Reporting of HO depends on the centre where it is diagnosed. In an intensive care unit the reported incidence is bound to be significantly lower than in a rehabilitation centre.

Post-traumatic HO formation can occur in any site, but most frequently in the hip following total hip arthroplasty. The hip is also the most common site of involvement in patients with a traumatic brain or spinal cord injury. The knee is less frequently affected. According to Horne & Blue (9) HO may occur both outside and inside the knee joint and is probably more common than previously assumed.

The incidence of HO following open reduction and internal fixation of acetabular fractures ranges between 18% and 90%.

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The initially strongly limited range of motion improves with time. In spinal cord-injured patients the incidence of HO is between 20% and 25% (7). In closed brain injury HO occurs in 10–20% of patients. In children and elderly people the incidence is significantly lower, but the reverse is true in children with severe burns (10–12).

Bruno (13) also stressed the wide variability. He distinguished between multiple injuries and nerve injuries, with a 20% overall incidence of HO, and found spasticity to be associated with HO formation. The incidence would be higher in a spastic limb. Studies conducted in Europe and Japan showed more divergent incidence rates (from 11% to 76%), strongly dependent on the methodology used.

HO is diagnosed about 4 months after a traumatic brain injury, cerebral haemorrhage, hydrocephalus, spinal cord lesion and near-drowning. The sex ratio does not differ, but the incidence of neurogenic HO is significantly lower in children than in adults. HO formation following total hip arthroplasty is most common in men (14). In children HO frequently resolves spontaneously (15, 16).

AETIOLOGY AND RISK FACTORS

The aetiology of HO is still unknown.

Race is not significantly correlated with the development of neurogenic HO (17, 18). The search for an association between HLA type and neurogenic HO has yielded little or no information. The literature data are divergent. A link between HLA-B18, B27 and DW7 has been reported (19–25). In subsequent publications only HLA-B18 was found to be associated with HO in nerve injuries. However, 75% of patients with neurological injury are HLA-B18 negative (19–25).

Ossification of the posterior longitudinal ligament has been linked with a genetic locus close to the HLA region on the short arm of chromosome 6p (26, 27).

A genetic predisposition has not yet been established. Research into genetic causes of HO could lead to a better understanding of the condition. Researchers have tried to find a link with fibrodysplasia ossificans progressiva (FOP) (28, 29), which is a rare autosomal dominant disorder, characterized by congenital malformation of the big toes and progressive mutilating HO in typical patterns. Jaimo et al. (30) studied the behaviour of bone morphogenetic proteins (BMP) and found an overexpression of BMP-4, a potent osteogenic morphogen. Closer investigation did not reveal a mutation in the BMP-4 gen. However, in physiological circumstances, the effects of BMPs are highly regulated by negative feedback from the antagonists noggin, gremlin, follistatin and chordin. A paresis of this inhibitory response, resulting in an overexpression of BMP-4 and a subsequent increased differentiation of osteogenic cells has been advanced as a cause of FOP. Further knowledge of this and other pathways can lead to new insights into the treatment of HO (30). HO can occur after routine diphtheria tetanus pertussis (DTP) immunizations in children with fibrodysplasia ossificans progressiva, whereas this is not the case with measles, mumps, rubella, hepatitis B or Haemophilus influenzae vaccinations. Also, subcutaneous injection poses no risk of HO formation (31).

Much research has been done into specific trigger mechanisms relating to metaplasia. Histologically, HO cannot be differentiated from callus formation of a healing fracture. The onset of the ossification process lies in fibroblastic metaplasia. There is a well-delineated zone of fibroblastic proliferation, followed by chondroblasts and eventually osteoblasts with blood vessels and Haversian canals.

Haemorrhage might be an important precipitating factor in the occurrence of HO, but repeated injections of blood into the quadriceps muscle of rabbits did not provoke radiological changes.

Michelsson et al. (32, 33) stressed the importance of the inducing agent in ectopic bone formation. In an experimental study of osteoarthritis, in which the hind limbs of rabbits were immobilized and daily exercised, they detected ectopic bone formation in the quadriceps. The authors postulated that immobilization and forcible mobilization are the most important triggers of heterotopic bone formation. This combination often underlies the pathogenesis of human HO. These factors are present in patients with paraplegia, severe burns, or severe multiple injuries treated with, for example, arthroplasty (32–34).

Traumatic myositis ossificans resembles HO, but is misleading. According to Subbarao & Garrison (11) haemorrhage oedema, osteoporosis surrounding HO and muscle necrosis are consequences rather than causes of HO formation (11). Shehab et al. (10) confirmed the hypothesis that soft-tissue ossification differs fundamentally from metastatic and dystrophic soft-tissue calcifications.

Already in 1971, Craven & Urist (35) reported transformation of primitive mesenchymal cells, present in the soft tissues of the fascia, into osteogenic cells to be the pathogenesis of HO.

Chalmers et al. (36) described 3 conditions necessary for HO formation: osteogenic precursor cells, inducing agents and a permissive environment. This would trigger the transformation of mesenchymal cells into bone-forming cells (48). This differentiation is induced by the BMP (37).

A genetic predisposition may also be implicated in the overall incidence of HO. Particularly in ankylosing spondylitis, hypertrophic osteoarthrosis and diffuse idiopathic skeletal hyperostosis, bone formation is increased with a higher risk of HO (38).

Men are at a higher risk of developing HO than women and also form a larger amount of bone. (39, 40)

Patients with a history of documented HO who underwent a total hip arthroplasty, are more prone to HO formation (38, 41, 42).

PATHOPHYSIOLOGY

Important contributing factors include hypercalcaemia, tissue hypoxia, changes in sympathetic nerve activity, prolonged immobilization, mobilization after prolonged immobilization

and disequilibrium between parathyroid hormone and calcitonin (10).

The initial stage of HO is accompanied by venous stasis and arteriovenous shunting in the involved tissues. Metabolic and vascular changes resulting from autonomic nervous system alterations might play a major role in HO metaplasia (43).

Eicosanoids (e.g. prostaglandins, leukotrienes) are important factors in bone metabolism. Prostaglandin E2 (PGE2) induces a dose-dependent increase of periosteal lamellar bone formation. Subcutaneous injection of PGE2 in growing rats induces heterotopic bone formation. The angiogenetic and vasodilating effect of PGE2 is well-known and would also stimulate collagen synthesis.

PGE2 excretion in 24-hour urine is a valuable indicator of early HO (38–42). An increase in serum creatine kinase and in 24-hour urinary hydroxyproline has also been described in spinal cord-injured patients with HO formation (43, 49, 50). Contrary to the findings in adults, alkaline phosphatase (AP) levels are not elevated in children during the development of HO (16).

The longer the duration of immobilization and the more frequent the periods of exercising, the higher the grade of heterotopic bone formation. Vigorous ranging of joints after 5 weeks of mobilization also resulted in HO, but to a much lesser extent. Repeated deep incisions or severe crush injuries caused little or no HO formation. Only some calcifications were observed. Particular care should be taken when exercising stiffened human joints. This is essential in the prevention of HO (32).

HISTOLOGY

Myositis ossificans and HO are fundamentally different.

An important step in the ossification process is fibroblastic metaplasia. Histological studies clearly demonstrated a zone of fibroblastic proliferation, followed by chondroblasts, which eventually transformed into osteoblasts with blood vessels and Haversian canals.

Michelsson & Rauschning (32) found that repeated forcible exercising of an immobilized knee induced HO formation in a rabbit quadriceps. However, when the position of the knee joint was changed during manipulation, the location of HO formation also changed.

In HO mature lamellar bone is observed peripherally, surrounded by a capsule of compressed muscle fibres and connective tissue. Oedema, hypersensitivity, muscle necrosis, and osteoporosis around HO are consequences rather than causes of HO. It is suggested that bone forms in connective tissue between muscle planes and not in the muscle itself. The new bone may be contiguous with the skeleton, but does not involve periosteum. Mature HO shows cancellous bone and mature lamellar bone with blood vessels and bone marrow, with only a small amount of haematopoiesis.

Lotta et al. (51) described microvascular changes associated with HO formation in paraplegics. These changes could be consequent upon a hypoxiemic condition in periarticular soft tissues, which could lead to metabolic changes that may in turn contribute to the development of HO.

DIAGNOSIS AND INVESTIGATIONS

The clinical examination already provides important diagnostic information. Increased joint stiffness, a limited range of motion, warmth, swelling and erythema are the principal clinical signs of HO.

It is often difficult to differentiate early HO from deep venous thrombosis (DVT), because the symptoms (swelling and erythema) may be similar. They are mainly observed in patients with spinal cord injuries and brain injuries. HO and DVT are frequently associated because of their mass effect and local inflammation. However, due to swelling and venous compression, HO may give rise to phlebitis (52).

Initially, the swelling can easily be localized. In later stages the oedema becomes indurated and a mass can be palpated. The clinical signs and symptoms of HO can develop from 3 to 12 weeks after a musculoskeletal injury, spinal cord injury, or another precipitating factor. Subsequently, distal to the lesion oedema can be present secondary to venous compression from HO. The early inflammatory stage may mimic cellulitis, thrombophlebitis, osteomyelitis, or a tumourous process (53–56). Intra-articular fluid is sometimes found, with secondary increased spasticity or fever.

The ancillary investigations include the assessment of AP levels and bone scintigraphy (43, 57, 58). Four weeks post-injury AP levels may reach 3.5 times the normal value, with a peak concentration around the 12th week. If HO formation is small, AP levels may remain unchanged. This is a good parameter in the absence of fractures. AP levels may also rise in case of fractures and liver disorders. AP determination is used in the diagnosis and follow-up of HO. An increase heralds functional transformation of mesenchymal stem cells into chondrocytes (59). The importance of hydroxyproline and creatine kinase has already been discussed.

Three-phase bone scintigraphy

Three-phase bone scintigraphy is used for both diagnostic and therapeutic follow-up purposes, and is the most sensitive imaging modality for the early detection of HO. The first 2 phases are indicative of hyperaemia and blood pooling, which are the precursors of an ossification process. Bone scintigraphy is usually positive after 2–4 weeks. It can also be used to assess the maturity of HO. Serial bone scans are used to monitor the metabolic activity of HO so as to determine the optimal timing for surgical resection, and to predict postoperative occurrence (12, 60–63).

Radiography, magnetic resonance imaging and computer tomography scan

Radiography, magnetic resonance imaging (MRI) and computer tomography scan (CT) have low specificity in the early stage of

HO. Before surgery, MRI and CT are valuable to assess the relation with blood vessels and peripheral nerve structures. Angiography is rarely used for the diagnosis of HO, but may aid in delineating important vessels in case of massive HO.

Prostaglandin E2 excretion in 24-hour urine

PGE2 excretion in 24-hour urine is felt to be a reliable bone marker not only for the early detection, but also for determining treatment efficacy. A sudden increase in 24-hour urinary PGE2 excretion would be an indication to perform bone scintigraphy. Monitoring could be done clinically and by measurement of 24-hour urinary excretion. HO is demonstrable on radiographs from 4 to 6 weeks post-injury.

Ultrasonography

Ultrasonography detects HO sooner than does conventional radiography (64, 65). Local signs of inflammation in spinal cord-injured patients are suggestive of HO (66–68). Ultrasonography is the best investigative modality not only for the early identification, but also for the follow-up of HO. It also has high sensitivity and specificity for the early diagnosis of HO 1 week after total hip arthroplasty (69).

PREVENTION

Rehabilitation

Much controversy exists on the use of range-of-motion exercises. Michelsson et al. (32, 33) demonstrated that forcible manipulation in rabbits induced heterotopic bone formation. More gentle exercising below the pain threshold, e.g. by means of continuous passive motion, maintains and even improves joint mobility and reduces spasticity, with no effect on bone formation. The better physical condition of the patient may postpone further treatment or even make it unnecessary (25, 70).

To date, most studies have been performed on rabbits. Only a few studies concern patients with central nervous system disorders. Even though gentle exercising of the joint within the pain-free range appears to be useful, further research remains mandatory.

Drug treatment

The prophylactic effect of indomethacin following total hip arthroplasty is generally accepted. Its action is two-fold: firstly, it exerts a direct effect through inhibition of the differentiation of mesenchymal cells into osteogenic cells; secondly, it has an indirect effect through inhibition of post-traumatic bone remodelling by suppression of the prostaglandin-mediated response (10, 25, 71).

Banovac et al. (71) conducted a randomized, prospective, double-blind, placebo-controlled clinical trial on its effect after spinal cord injury. Thirty-three paraplegic and tetraplegic patients were divided into 2 groups. Group I was treated with indomethacin 75 mg/day, group II received placebo. Both groups were treated for 3 weeks and were matched for age, number, severity of spinal cord injury, and time interval between injury and start of the study. All patients received misoprostol orally 200 mg/day for the prevention of gastric ulcers. Because of its abortive potential, women were excluded from the study. Bone scintigraphy was performed for the early detection of bone formation. In the event of a positive bone scan, the patient was withdrawn from the study and treated with etidronate (a biphosphonate) for 6 months.

An early stage of HO was demonstrated in 4 patients of the NSAID group (25%) and in 11 of the placebo group (65%); this difference was significant ($p < 0.001$). Moreover, bone formation was significantly more delayed in the NSAID group (32 ± 7 days vs 19 ± 11 days, $p < 0.5$) and the inflammatory signs (swelling, redness and fever) were significantly less. Late bone formation, i.e. radiographically visible, occurred in 12.5% of the NSAID group and in 41% of the placebo group ($p < 0.001$). Remarkably, only half of the patients in the placebo group presented a solitary localization, while the other half had involvement of 2 or more joints. After administration of indomethacin only solitary joint involvement was found with significantly less bone formation.

A recent comparative study between celecoxib and indomethacin for the prevention of HO following total hip arthroplasty showed a similar result with significantly less side-effects (72).

In addition to indomethacin, research was also conducted into possible beneficial effects of methylprednisolone, verapamil, warfarin and calcitonin, but none of these compounds were conclusively found to be of added value in humans (25).

Radiation therapy

As with indomethacin, the prophylactic effect of irradiation after total hip arthroplasty or resection of HO is generally accepted, but literature data on its efficacy in patients with brain and spinal cord injuries are still non-existent.

Esenwein et al. (59) studied the effects of a single dose of 7 Gy vs fractionated irradiation of 5×2 Gy (which are equivalent doses according to Ellis' principle) on the suppression of heterotopic bone formation. To this end an allogenic bone matrix had previously been implanted in 50 rats to induce bone growth. Radiological and histological evaluation, and calcium measurements by flame photometry showed suppression to be significantly better after fractionated radiotherapy. This difference could not be demonstrated in earlier studies.

TREATMENT

Drug treatment

The action of biphosphonates is threefold: inhibition of calcium phosphate precipitation, slowing of hydroxyapatite crystal aggregation, and finally inhibition of the transformation of calcium phosphate to hydroxyapatite. Mainly the use of sodium etidronate has been studied. The inhibitory effect on bone

formation is thus limited to only the crystallization process; bone matrix formation remains unaffected. After cessation of treatment the matrix undergoes uninhibited mineralization, known as the "rebound-effect". Consequently, it is essential to start treatment as soon as possible and continue it for a sufficiently long period of time, i.e. at least 6 months (10, 25, 73).

Banovac et al. (73) studied 40 patients 2–5 weeks following a spinal cord injury. All patients presented clinical and scintigraphic evidence of early HO. The radiological findings were negative. They were treated with etidronate, 300 mg/day intravenously for 3 days, followed by 20 mg/kg/day orally for 6 months. A clinical and radiological follow-up was performed every 6–8 months. Eleven patients (27.5%) developed HO 1.5–2 years after treatment, grade 1 in 8 of them and grade 2 in 3 (6). Grades 3 and 4 were not observed. However, of these 11 patients, only 2 (5%) had scintigraphic evidence of HO. The remaining 9 patients presented *de novo* formation of ectopic bone. The authors concluded that rebound ossification after early and prolonged administration of etidronate is rare; new HO foci show a milder course without severe functional impairment, and total joint ankylosis does not occur. However, it is difficult to establish whether a true rebound of the initial early scintigraphic diagnosis was concerned here, or rather *de novo* formation of heterotopic bone.

In any case treatment with biphosphonates appears to be effective as long as it is continued. It only retards osteoid calcification because ossification continues when the biphosphonates are stopped. This is actually not a true "rebound" effect; it is merely the physiological process that progresses. Therefore, biphosphonates are no longer used in the prevention of HO (74, 75).

Radiation therapy

Irradiation interferes with the differentiation of pluripotent mesenchymal cells to bone precursor cells. Its prophylactic effect after hip surgery is well known, but its use in the treatment of central nervous system disorders is insufficiently documented. Sautter-Bihl et al. (76) irradiated 46 joints in 36 patients. The mean duration of follow-up was 23.6 months (4–98 months). Three patients were lost to follow-up. The diagnosis was made on the basis of the clinical examination, bone scanning and computed tomography. All patients presented an early stage of HO; sometimes small bone islands were visible. Eleven patients had manifest ossifications, which were resected prior to irradiation. A dose of 10 Gy in fractions of 2–2.5 Gy was administered, except in 3 patients who received a total dose of 12–20 Gy. Of the 32 primarily irradiated joints, 16 showed no additional radiological abnormalities: only 3 showed progressive bone formation. No significant differences were seen in the postoperative group (11 joints). Also, no difference was found between single-dose or fractionated radiation therapy.

A moderate increase in bone formation was observed in only 3 patients ($<10\%$), in whom timing of treatment had not been optimal, i.e. as soon as possible after the onset of symptoms. This study is flawed by lack of standardization. Different radiation doses were administered, single-dose or fractionated, both as a primary treatment and after surgery. Moreover, not all patients had the same grade of HO. Further investigation using stricter population criteria is mandatory.

DISCUSSION

The currently available treatments are still highly controversial. As primary prevention, risk factors such as pressure ulcers, deep venous thrombosis and limb contractures should be avoided. Rehabilitation can play an important role not only in the prevention of contractures but also in the maintenance of a good physical condition, obviating the need for additional treatment. Importantly, forcible ranging of joints can induce microtrauma and haemorrhages, which may increase HO formation. Recent studies have shown a favourable effect of active and passive exercising of joints within the pain-free range (25, 70).

The use of NSAID, particularly indomethacin, is generally accepted following total hip arthroplasty and as a secondary preventive measure after resection of HO. Indomethacin also appears to be effective in the primary prevention of HO after spinal cord injuries. A reduction in both the early (clinical and scintigraphic) and late (radiological) diagnoses was observed (72).

With the new subgroup of COX-2 inhibitors similar results have been achieved with less side-effects, but valid conclusions cannot yet be drawn because of insufficient research data (73).

Etidronate has since long been used to treat HO. Biphosphonates have no effect on bone matrix formation, resulting in frequent recurrences of the condition after cessation of treatment. Early institution combined with a prolonged treatment duration and higher doses significantly reduces this rebound effect. An early diagnosis is of crucial importance and etidronate has to be continued for 6 months. A dose of 300 mg intravenously for 3 days, followed by 20 mg/kg/day appears to be effective (10, 25, 73).

Biphosphonates have no effect on bone tissue that has already been formed. If HO develops despite treatment, it is less severe and of little clinical relevance. Side-effects mainly consist of gastrointestinal symptoms. Serious side-effects such as hyperphosphataemia, osteomalacia or spontaneous fractures have not been reported.

The exact mechanism of action of radiation therapy is unknown. It has been suggested to interfere with the differentiation of pluripotent mesenchymal cells into osteoblasts. Irradiation also diminishes the pain perception by suppression of the tissue inflammation and ablation of the pain receptors (25, 73). Since the 1970s this treatment has also been generally accepted as prevention of HO following total hip arthroplasty. Sautter-Bihl et al. (76) were the first to use radiation therapy in early stages of HO after spinal cord injury. Progression of bone formation was seen in less than 10% of the patients. No significant difference was observed between single-dose and fractionated administration. This contrasts with the study of

Esenwein et al. (59), who obtained a markedly better effect after fractionated irradiation, at equivalent doses, in rats following the induction of HO.

No relevant side-effects of radiation therapy were observed. Possible late side-effects are radiogenic tumour induction and fertility problems. However, the risk of tumour induction at doses less than 30 Gy is small. Currently, surgery is the only treatment that is capable of removing already formed bone, but complications frequently occur: deep venous thrombosis, infections, pressure ulcers and major blood loss (25, 77). Moreover, monotherapy is associated with an extremely high recurrence rate. Radiologically the recurrence rate is 82% to 100%, clinically 17–58% (25). Consequently, surgical resection must always be combined with NSAID or postoperative radiation therapy. Indications for surgery include improvement of the range of motion, e.g. to enable patients to sit properly, reduction of contractures, prevention of pressure ulcers and intractable pain. The optimal timing of surgery is still controversial. Usually it is suggested to wait until complete maturation of the ectopic bone, mainly to avoid recurrences. Maturation is manifested by normalization of the scintigraphic findings and usually takes 12–18 months. There is a growing tendency to pay more attention to the patients neurological condition and to delay resection until he or she is maximally recovered from his brain or spinal cord injury.

Pre- or postoperative single-dose or fractionated (5 doses) irradiation is effective in the prevention of HO in risk patients (78, 79).

Irradiation diminishes the bone ingrowth and the strength of fixation of porous implants. Protection of the prosthetic implants may reduce this risk (80).

At Ghent University Hospital we have a slightly different approach to the secondary prevention of HO. Prior to total hip arthroplasty or resection of HO single-dose radiation therapy is administered once. An NSAID is given after surgery. The rationale of this irradiation is to reduce peroperative and postoperative bleeding and in this way also the development of HO. Postoperative irradiation is not applied.

In conclusion, HO is a frequent and potentially very serious complication following central nervous system disorders, multiple injuries, surgery and burns. The patients daily functioning may be severely compromised by loss of adequate posture, impaired function of the extremity, pressure ulcers and deep venous thrombosis.

In addition to the treatment, prevention of HO is of paramount importance. First of all, proper attention should be paid to the presence of predisposing factors such as muscle contractures, pressure ulcers and infections.

From the earliest clinical signs of HO and after confirmation by technetium bone scintigraphy has been obtained, NSAID and radiation therapy can inhibit the pathological process and prevent the formation of mature bone. Indomethacin is the most commonly used NSAID. The new-generation COX-2 inhibitors seem to have the same beneficial effect with less adverse reactions. However, this should be documented by further studies. Also, no consensus has yet been reached on whether or not to fractionate radiation therapy.

Early diagnosis of HO is essential in the treatment with biphosphonates. To avoid rebound ossification the treatment should be started early, at high doses, and continued for a longer time than previously assumed. A dose of 300 mg IV for 3 days, followed by 20 mg/kg/day for at least 3 months is recommended.

In case of severe functional impairment or intractable pain, surgical removal can be considered. The optimal timing for surgery is still controversial, but the tendency is to attach more importance to the functional and neurological recovery, rather than to the maturity of the bone. One should realize that surgical resection is often associated with complications and a high risk of recurrence. Secondary prevention by means of radiation therapy and/or administration of NSAID is essential.

The focus of the research into HO has mainly been on its occurrence after total hip arthroplasty. More and more attention is being paid to the neurogenic form, which has the same preventive and therapeutic possibilities, with documented effects. Research into the aetiology and physiopathology of this disorder should be continued to search for causal therapies.

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