

Pathophysiology and Etiology of Neurogenic Heterotopic Ossification

Nörojenik Heterotopik Ossifikasyonda Patofizyoloji ve Etiyoloji

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Summary

Neurogenic heterotopic ossification (NHO) is the formation of pathological bone tissue in the soft tissues around joints after neurological injury, where ossification is not observed normally. This condition, frequently seen in patients with spinal cord injury (SCI) and traumatic brain injury (TBI), can cause complications such as severe limitation of motion, difficulty in daily living activities, nerve compression and pressure ulcers. NHO etiopathogenesis was reviewed with current literature, to enlighten the research studies planned on treatment and the precautions to prevent it. Etiology of NHO is not completely revealed in patients with SCI and TBI, however humoral, neural, immunological and local factors probably play a role in the pathophysiology. In patients with SCI, complete lesion, immobilization, exercise, microtrauma and proprioceptive alterations may possibly take a role in NHO development. The most important risk factors for patients with TBI are: spasticity, prolongation of coma state more than 2 weeks, immobilization, fractures of long bones, limitation of range of motion, infection, and development of autonomic dysregulation. However, it is not known which of the factors affect the severity and the long-term outcomes of the disease. Considering the etiopathogenesis of NHO, it is concluded that more comprehensive studies are needed to detect and prevent the risk factors before it develops, to determine the type of therapeutic exercises and the suitable timing of exercises. *Türk J Phys Med Rehab 2010;56:81-7.*

Key Words: Neurogenic heterotopic ossification, spinal cord injury, traumatic brain injury

Özet

Nörojenik heterotopik ossifikasyon (NHO), nörolojik bir hasar sonrası normalde kemikleşmenin görülmeyen eklemlerin çevresindeki yumuşak dokuda patolojik kemik doku oluşumudur. Omurilik yaralanması (OY) ve travmatik beyin hasarı (TBH) olan hastalarda sık gözlenen bu durum, ciddi düzeyde hareket kısıtlılığı, günlük yaşam aktivitelerinde güçlük, sinir basıları ve baskı yaraları gibi komplikasyonlara neden olabilmektedir. NHO oluşmadan önce alınabilecek önlemler ve tedavilere yönelik planlanacak araştırmalara ışık tutması amacıyla, NHO etiopatogenezini güncel literatürün eşliğinde gözden geçirildi. OY'li ve TBH'li hastalarda NHO'nun etiyojisi tam olarak bilinmemekte, ancak patofizyolojisinde hümorale, nöral, immünolojik ve lokal faktörler muhtemel rol oynamaktadır. OY'li hastalarda, yaralanmanın komplet olması, immobilizasyon, egzersiz, mikro-travma ve proprioseptif duyu bozukluğunun NHO gelişiminde olası rolleri bulunmaktadır. TBH olan hastalarda ise en önemli risk faktörleri; spastisite, koma halinin 2 haftadan uzun sürmesi, immobilizasyon, uzun kemik kırıkları, eklem hareket açıklığında kısıtlılık, enfeksiyon ve otonomik disregülasyon gelişimidir. Ancak hangi faktörün hastalığın ciddiyetini veya uzun dönem sonuçlarını etkilediği bilinmemektedir. NHO'nun etiopatogenezini göz önüne alınarak, risk faktörlerinin belirlenerek oluşmadan önce önlenmesi, tedavi edici egzersiz tiplerinin ve uygun zamanlamanın tespitine yönelik daha kapsamlı çalışmalara ihtiyaç olduğu sonucuna varıldı. *Türk Fizik Tıp Rehab Derg 2010;56:81-7.*

Anahtar Kelimeler: Nörojenik heterotopik ossifikasyon, omurilik yaralanması, travmatik beyin hasarı

Introduction

Neurogenic heterotopic ossification (NHO) is a pathological formation of new bone tissue in muscle and connective tissue, where normally ossification does not occur, following a neurological injury (1). Heterotopic ossification (HO) occurs in

10% to 53% of patients with spinal cord injury (SCI) and in 10% to 40% of those with traumatic brain injury (TBI), and consequently severe joint movement restrictions develop in 18% to 35% of patients with SCI and in 8% to 10% of those with TBI (1-5).

The pathophysiology of HO is multifactorial and complex, and could not have been explained thoroughly for years. It is

suggested that three circumstances, including osteogenic precursor cell, an inducing agent and tissues predisposing osteogenesis, are required for the formation of HO (6).

It is known that this complication, frequently encountered in patients with either SCI or TBI, requires surgical removal when it leads to complications such as severe movement restrictions, difficulty in activities of daily living, nerve compressions and decubitus ulcers; and that there are risks of fracture and recurrence even after surgery. Therefore, the genesis and etiopathogenesis of NHO were reviewed with the current literature for enlightening the studies directed towards the prevention of its formation and the development of therapeutic strategies.

Heterotopic Ossification in Patients with Spinal Cord Injury

HO incidence is reported to be ranged between 10% and 53% depending on the study design, diagnostic methods and diagnostic criteria used in the studies in patients with SCI (1-3,7). NHO occurs less in non-traumatic myelopathies (6-15%) compared to traumatic ones and in children (3-10%) compared to adults (8,9). The symptoms in children are not different from those in adults, but less evident. Spontaneous regression occurs more frequently in children and young adults compared to elderly patients (9). The clinical appearance ranges from an asymptomatic situation found on direct radiographs to severe joint restrictions, and even ankylosis. NHO leads to restriction in the range of joint motion (ROM) in 18% to 35% of the patients, whereas ankylosis may develop in 3% to 8% of the patients (1-3). NHO develops under the SCI level and is most frequently seen at hip joint (70-97%), followed by knee, elbow, shoulder, hand and spine, in order of frequency (2,10). The limitation of hip ROM causes loss of adequate sitting, pressure sores, pain and functional restrictions in activities of daily living (11). The low neuropathy rate due to HO, despite the fact that HO may compress adjacent vessels and nerves in the patients with SCI, is associated with the sensory loss already existing in complete patients (1). NHO is often diagnosed in the second month, generally within the first 6 months after SCI; however, it is reported that NHO may develop years after the SCI (2).

Pathophysiology

NHO originates from the connective tissue lying between the muscles, outside of the joint capsule. The joint space and capsule are preserved. It may be contiguous with the bones, but does not involve the periosteum. Muscle fibrils are not mainly involved, but they may be compressed by calcified soft tissue and local muscle necrosis may develop (1).

NHO begins as an oedematous inflammatory reaction with an increased blood flow in the affected soft tissue area. First, exudative cell infiltration takes place. Then, fibroblastic cell proliferation occurs followed by osteoid formation and finally bone matrix development is seen. Within the first 2 weeks, primitive bone foci are observed as small masses in the fibroblastic mesenchymal reaction area, primarily in the periphery. Osteoblasts produce tropocollagen, which is a polymerized form of collagen and synthesize alkaline phosphatase (AP). AP degrades pyrophosphate, which is a compound that prevents calcium deposition. The newly developing ectopic bone matrix inactivates nearby pyrophosphate. Therefore, AP allows precipitation of calcium and mineralization of bone matrix (12).

Mineralization process of soft tissue includes a gradual precipitation of hydroxyapatite crystals. In the maturation process of HO, the primitive bone is matured by time and the lamellar bone is formed from the periphery towards the center. The maturation of the bone is generally completed within 6-18 months. Mature NHO mimics normal bone both radiologically and histologically and includes Haversian canals, cortex, blood vessels and bone marrow with a very low amount of hematopoiesis (1,6).

Three circumstances should be met to form HO: osteogenic precursor cell, an inducing agent and an appropriate environment consisting of the tissues predisposing osteogenesis (6). Although the mechanism of NHO has not been known exactly yet, humoral, neural and local factors are likely to play a role in its pathophysiology (Figure 1). There is either a migration of the remote mesenchymal cells to the affected area and their transformation into osteoblasts, or a transformation of local mesenchymal cells directly into osteoblasts. It is unknown whether these cells migrate randomly or as a response to certain chemotactic factors, but it is reported that many factors are of importance in the transformation of the mesenchymal cells into osteoblasts (1).

Humoral Factors

In studies on sera from patients with SCI, it has been shown that humoral mechanisms can be effective (10,13). In a study, investigators incubated the sera of the SCI patients with and without HO at the 4th to 7th months after the injury and the sera of normal individuals with human osteoblasts in tissue culture, and they found an increase in osteoblast-stimulating factor in the patients with SCI, which was more prominent in the patients with HO (13). In the study by Renfree et al. (10) the sera of patients with SCI were incubated with osteoblasts of fetal rats 12 weeks after the event, a significant increase in serum mitogenic activity was observed, but no significant difference was found when the patients with HO were compared with the other patients and healthy controls. The results suggest that the increase in mitogenic activity may indirectly play a role in the process stimulating the bone formation.

Although humoral factors play a role in the process of stimulation of bone formation in patients with SCI, their genesis and biological features are still unknown. However, with the experimental studies on in vitro ectopic bone formation, an inducing protein for bone formation released by demineralized bone tissue has been identified. This protein is called bone morphogenetic protein (BMP) (11). These morphogenetic proteins play a critical role not only in HO pathogenesis, but also in normal embryo growth. During the growth of the embryo, BMPs specialize in many tissue types and play a role in the differentiation of bony structures as well as connective tissue. The effectiveness of BMP in osteogenesis during the fracture healing process has been shown (14). Another protein group is also important in the regulation of the effects of BMPs. These proteins are BMP receptors and BMP antagonists. A deficiency of these proteins will cause an increase or a decrease in the effects of BMPs.

Moreover, a potential bone resorption and collagen destruction occurred in patients with SCI may play a role in the emergence of some osteogenesis-inducing factors not defined yet exactly. In the NHO pathogenesis, it is proposed that non-collagen proteins play a role and that fibroblasts take over the role of osteoprogenitor cells (15).

Neuro-immunological Factors

Neural effect on the development of NHO should be regarded. It is suggested that the damage of the intermediolateral sympathetic column after SCI may lead to autonomic dysfunction and subsequently to HO. In contrast, the continuous exposure to neurogenic irritation is proposed as a central factor in situations in which some of the fibrils of the intermediolateral tractus remained intact (6). Recently, vascular and metabolic changes, resulted from the injury of the autonomic nervous system, are reported to take place in the etiology of HO (1). The dysfunction of sympathetic system causes local microvascular changes in the affected tissues, arterio-venous shunt and increased vasculature, vascular stasis, oedema and prolonged sweating (7). In a study on biopsy from paraplegic patients by Lotta et al., alterations were determined in the endothelial cells and in the capillary basal membrane in the cutaneous and subcutaneous tissues near the HO region (7). It is not known whether these changes occur as causes for or secondary to NHO. The hypothesis that the disruption of the neuro-immunological pathways causes the development of NHO by deteriorating the balance between the osteoblasts and the osteoclasts is still accepted. Regardless of its reason, the presence of interstitial oedema, whether due to a deteriorated autonomic regulation, hypersensitivity or hypoproteinemia, provides a suitable environment to trigger the pathological calcification of the bone (1).

Furthermore, the cessation of signals from the proprioceptive receptors below the lesion level in patients with SCI leads to absence of detection of these signals by the somatosensory areas placed in the anterior parietal cortex. The signals are

interrupted in the way following the dorsal root ganglion. The spinal cord loses its ability to control below the lesion level. Consequently, the tissues become more vulnerable to trauma. When there is an interruption in the neuronal network based on the data from the receptors placed in the ligaments and muscles, ectopic bone formation can occur (16).

Local Factors

Local factors predisposing to NHO are venous thrombosis, hemostasis, infection, pressure sore and microtrauma. These factors lead to tissue damage and inflammation, and consequently to tissue hypoxia, and cause ectopic bone formation by providing a suitable environment or by adding humoral factors to the inflammatory process. In this instance, the inflammatory factors such as prostaglandin-E2 (PG-E2) and interleukin-1 (IL-1) play a role. Animal studies show that PG-E2 has angiogenic and vasodilator effects and increases the periosteal lamellar bone production dose-dependently along with IL-1 (17). Additionally, it was shown that a subcutaneous PG-E2 injection administered to rats could lead to HO (18). In another study, abnormalities in PG-E2 levels in 24-hour urine samples from patients with SCI were observed (3). However, it is difficult to interpret the PG-E2 level in the SCI patients who have urinary tract infection or sperm discharge in urine. The fact that these two groups constitute the majority of patients with SCI makes difficult to understand the mechanism of action of PG-E2.

Genetic Factors

Generally, no association between NHO and race was found. However, higher rates in favour of young men have been reported in some studies (1). A genetic predisposition to NHO

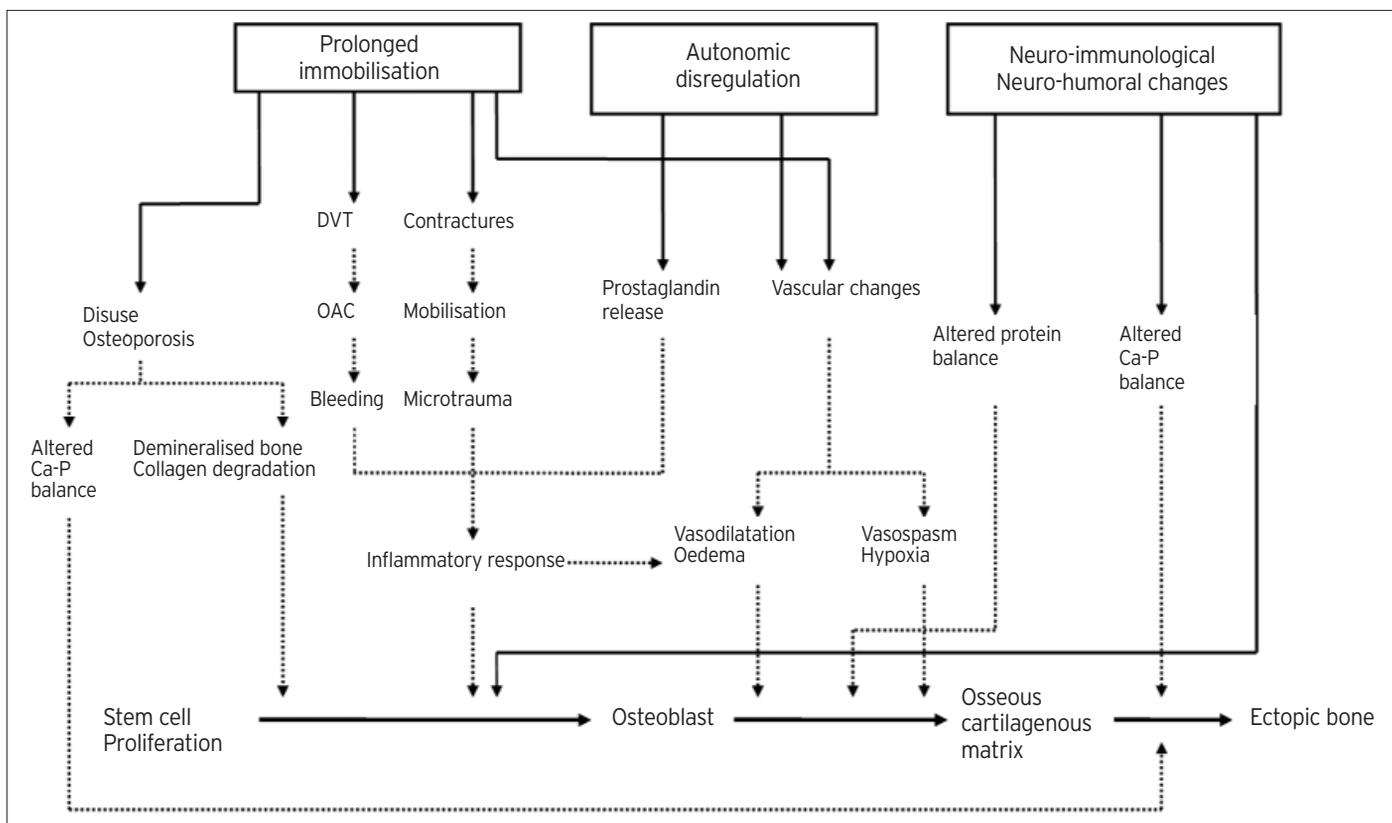


Figure 1. The pathophysiology of heterotopic ossification in patients with spinal cord injury. DVT: deep venous thrombosis, OAC: oral anti-coagulant (1) Van Kuijk et al. Neurogenic heterotopic ossification in spinal cord injury. Spinal Cord 2002;40: 313-26.

related to the human leukocyte antigen system (HLA) is reported. Despite the opinion supporting an association between HLA-B18, HLA-B27 and NHO, there are studies suggesting no association (19,20).

Clinical Risk Factors

Clinical factors related to NHO are lesion level and severity, exercises, deep venous thrombosis (DVT), spasticity, pressure sore and urinary tract infection (UTI) (1,2,8,11,21-29).

Lesion level and severity: NHO is more frequently seen in patients with inferior cervical or upper thoracic lesions; however, the completeness of the lesion seems to be more important than its level (11,21). Although no association between NHO and the severity of the motor deficit was found in only one study (22), it has been shown in many studies that complete SCI is more commonly associated with HO compared with incomplete SCI (1,2). HO is less frequently encountered in patients with lumbosacral or cauda-conus lesions, which have high ambulation rates (21).

Exercises: The repetitive forced passive motion exercises, performed on the joint to protect the ROM, harm the soft tissue and initialize this pathological process. The microtraumas in the soft tissues resulted from forced passive exercises and muscle weakness (imbalance) create a mechanical stress at the muscle-tendon junction. Microtrauma leads to new bone formation by causing secretion of osteoblast-stimulating factor through inflammatory response or directly (1). In a study, clinical HO development was defined in a group of patients in whom passive exercises were started only seven or more days after SCI (27). Studies performed on rabbits show that HO could develop by forced passive movements in paralytic extremities that had been immobilized for a prolonged period (28). It is also remarkable that hip, which is the most involved region, is the region to which the stretching exercises are commonly applied. The duration between SCI and the start of passive ROM exercises is encountered to be another risk factor for HO development (27). Silver (29) denotes that a deformation in the elasticity of joint capsule, shortening in muscle length, adhesions in ligaments, fascia and capsule, and contracture can be developed if passive movements are not implemented from the day of the injury; and that initializing passive movements after these changes increases HO risk by leading to soft tissue damage.

DVT: The patients with traumatic SCI have the risk of thromboembolic events in the acute stage. Several studies show a strong association between DVT and NHO. Colachis and Clinchot (25) reported that the rate of association of DVT and NHO was 5.3%, the DVT diagnosis was made before HO diagnosis in all of the cases and HO developed on the same side where DVT had occurred. This finding indicates that DVT is likely to be a risk factor for HO. Perakash et al. (26) reported an increase in coagulation parameters correlated with HO developed in chronic SCI patients. Furthermore, a compression of vascular structures by local oedema and growth of ectopic bone may be another mechanism by which HO may predispose to DVT. However, the pathophysiological relationship between DVT and NHO is not entirely defined.

Spasticity: There is a controversy about the association between NHO and spasticity. In some studies, it is reported that HO is more common in SCI patients with spasticity and moreover, the severity of spasticity further increases the risk (2,8). Although the observations showing that HO is more

common in flask extremities or in those less affected from spasticity (23) indicate that spasticity predisposes to HO development, this association can be contrarily interpreted as NHO development causes more severe spasticity (1).

Pressure sore: The damaged soft tissue region becomes susceptible to ectopic bone formation by pressure sore and oedema. On the other hand, pressure sores can also be secondary to HO (1).

UTI: It can generate an antigenic source to start the immune response triggering NHO. Furthermore, bone demineralization accompanied by calcium loss and collagen loss in the acute phase of SCI may increase the risks of urinary tract stones, osteoporosis and NHO (23,24).

Heterotopic Ossification in Patients with Traumatic Brain Injury

NHO incidence after TBI varies from 10% to 40% (5,30,31). NHO is less common in non-traumatic central nervous system (CNS) pathologies compared to those which are traumatic (1,8,32). The severity of TBI is generally correlated with HO (30). In a study in 114 patients with severe TBI, clinical HO was determined in only 7.9% of patients. This low rate is correlated with the effectiveness of therapeutic programs such as immediate physiotherapy and botulinum toxin injections (33). However, NHO is significantly related to morbidity, although it is rarely seen. NHO causes pain, decrease in ROM, severe functional restriction (8-10%) and ankylosis (5%) (30). Hence, the better understanding of NHO etiopathogenesis will serve many patients.

Pathophysiology

Although the pathological mechanism underlying this process is not known thoroughly, it is known that an imbalance in bone cycle occurs because of the involvement of osteoblast differentiation. Osteocalcin has a regulatory role in osteoblast proliferation. Typically, lower osteocalcin levels induce osteoblast proliferation in early proliferation stage, while higher osteocalcin levels prevent excessive mineralization at the end of mineralization. In a study performed, it was reported that lower osteocalcin levels determined in patients with TBI could play an important role in the development of HO (34).

The bone created in post-TBI, NHO is histologically and radiologically similar to mature bone and is distinguished from a simple calcification by its osteoblastic capacity. Accumulation, proliferation and differentiation of progenitor cells occur as in typical ossification. Subsequently, osteoprogenitor cell maturation and osteoblast activation occur. Development of mature bone from soft tissue is observed. Increased vascularity in soft tissues is the first sign to be determined. Then, collagen fibrils are seen to be scattered among small foci of calcification (35). Extracellular matrix is mainly composed of type 1 collagen and is quickly mineralized after 3-4 weeks. An organized trabecular bone is formed after 6-12 months. If it is attained complete maturation, development of Haversian canals, blood vessels and medulla can be observed. There is an increased remodelling in heterotopic bone compared to the normal bone. Both osteoblast and osteoclast are increased in number by 50% to 300%, compared to those in the areas of normal bone production (30). The bone cycle in HO is shifted from a steady-state situation towards osteoblastic activity. Bone resorption may be impaired (36).

Humoral and Local Factors

Humoral mechanisms were shown to be responsible for the development of NHO in TBI patients. In a study by Binder et al. (37), it was revealed that serum obtained from patients with TBI augmented the effect of osteoblast-growing factor in fetal rats. Renfree et al. (10) incubated sera of TBI patients with the osteoblasts of fetal rats, 12 weeks after the event. A significant increase in serum mitogenic activity was observed, however, no difference was seen when the patients developed NHO compared with the other patients and healthy controls. Because the results obtained did not support the presence of humoral factor directly inducing osteoblast proliferation within the first 12 weeks, it was claimed that the increase in mitogenic activity could play an indirect role in the bone-inducing process.

Although "skeletal muscle stem cell" and "migrating osteoblastic cells" also play a role in the development of NHO, "mesenchymal stem cells" are accepted as the principal cell type (38). However, local environmental factors and the presence of osteogenic agents seem to have more priority in the development of NHO. Microvascular alterations that reduce the tissue oxygenation by changing the calcium content of the skeleton and local blood flow can be responsible for the NHO development (7). Moreover, hyperventilation used to reduce the intracranial pressure after TBI may cause respiratory alkalosis that predisposes to bone production. Experimentally, models showed that an increase in pH augmented the precipitation of calcium (30). Multiple trauma, generally accompanied by TBI, also leads to a decrease in collagen destruction and an increase in bone formation (36).

Neuro-immunological Factors

As in the patients with SCI, the loss of communication between periphery and CNS in TBI patients leads to ectopic bone formation by causing autonomic dysregulation, humoral and neural changes (1,39). Hendricks et al. (39) reported that autonomic dysregulation can increase the probability of HO development in patients with TBI. Moreover, as the proprioceptive receptors are not entirely under control, there will be an induction of bone formation. The interruption of the connection between joint and cerebellum or between somatosensory areas and posterior parietal cortex generates a suitable environment for irregular bone formation. Passive forced exercises create a trauma effect because of misunderstanding of proprioceptive receptors. Hence, it is accepted that HO is also associated with the proprioceptive defect in patients with TBI (16). This situation can be explained by the fact that the proteins inducing bone growth are not under control anymore.

Every type of pathologies that disrupts blood-brain barrier (BBB) causes release of osteogenic factors from CNS. The osteogenesis-inducing character of blood obtained from TBI patients, which has been demonstrated in many studies, supported the existence of humoral osteogenic factors in these patients. The increase in bone formation seen in NHO or fracture healing in patients with TBI confirmed the activation of osteogenic cells by osteogenic factors (40). In vitro evidence showed that osteogenic factors are in the systemic circulation (10,37,41-44). An association between callus formation and osteogenic factors in serum was also shown in vivo (41). Two studies investigating the osteogenic effect of CSF after TBI revealed that this fluid has osteogenic effect, namely, this

effect has central origin (42,43). However, in these studies human tissues were rarely used and etiologic agents could not have been explained thoroughly (10,37,41-44).

In a study on rats, it was shown that the number of bone marrow stromal cells (BMSC) in serum obtained 48 h after trauma from rats with TBI was decreased compared to control rats. AP levels measured simultaneously were found to be higher than normal. These findings show the effectiveness of humoral factors starting the maturation of osteoprogenitor cells 2 days after trauma (43). In a similar study performed on human serum, it was claimed that the serum of patients with TBI had proliferative effect on fetal rat calvarial cells (FRC) (37).

In a study by Boes et al. (41), the effect of sera from 23 rats with TBI and femur fracture on the proliferation of mesenchymal stem cells, fibroblasts and osteoblastic cells was compared with the effect of sera from 20 rats with only femur fracture. The serum of TBI group had a proliferative effect only on mesenchymal stem cells. An association between mesenchymal stem cell proliferation and callus formation was also shown. It was concluded that humoral factors were effective on early HO development and fracture healing by increasing mesenchymal progenitors after TBI.

In a study by Eid et al. (44), it was defined that the post-trauma sera obtained from 10 multiple trauma patients, seven of whom had TBI, caused a decline in human fibroblastic and osteoblastic cell groups and in apoptosis of BMSCs, and an increase in its proliferation 10 days after trauma. These events induce an increase in osteogenic cell number and consequently ossification. However, the fact that the patients evaluated in this study had multiple traumas out of TBI leads to the fact that these findings cannot be correlated with TBI only.

The results of a study performed by Renfree et al. (10) do not support the theory that sera obtained from the patients with TBI have augmenting effects on the growth of osseous cells. In this study, it was shown that the sera of TBI patients did not increase the proliferation of the calvarial cells of one-day-old rats. No difference in osteoblast number was determined between the patients with or without HO.

In a study investigating the effect of CSF in NHO, CSF was collected from four rats with TBI, 7 days after the injury. The study showed a decline in BMSC number and an increase in AP level in the rats exposed to CSF in both groups of TBI and controls. It was reported that the mineralization created by these two groups was greater than that seen in dexamethasone (control) group and CSF could support ossification (43). In another study on human fetal osteoblasts, CSF proliferation rate was shown to be significantly higher in individuals with TBI than those without TBI (42).

Numerous newer candidates have been nominated as centrally released humoral factors. Many factors affecting mesenchymal and osteoprogenitor cell proliferation have been determined in serum after TBI, however, the results are controversial, and ossification and CNS damage are linked to an accidental association (30). Interleukin-6, leptin, fibroblast-growing factor, growth hormone, insulin-like growth factor-1, prolactin and parathyroid hormone are the substances investigated and found to be ineffective (30,36,45). It can be said that the most promising candidate is the BMP family. It was shown that BMP could start bone formation in vivo and in vitro in animal models (46). As shown in cases with fibrodysplasia

ossificans progressiva, the disruption of BMP signals can cause HO development (47). However, their effects on ossification are controversial because of the fact that their systemic effects are limited despite their local importance (48).

Genetic Factors

In a study by Minaire et al. (19) investigating the presence of HLA antigens in 32 TBI patients, 23 of whom developed HO, it was reported that HLA-B 18 was not determined in the patients without HO. On the contrary, HLA-B 18 tissue antigen was determined in 25.7% of TBI patients who developed HO and in 7.6% of healthy controls. However, further studies did not support these findings (20).

Clinical Risk Factors

The most important risk factors defined for HO development in patients with TBI are spasticity, coma situation longer than 2 weeks, immobilization, extensive axonal damage, long bone fractures, restrictions in ROM, infection and development of autonomic dysfunction during follow-up (6,31,39,49-53). However, the effects of these factors on the severity of the disease and long-term outcome are unknown. Among these risk factors, only autonomic dysregulation was defined to have a strong predictive relationship with HO development (39).

In a study on 86 severe TBI patients by Hurvitz et al., it was determined that there was a significant association between the duration of coma and HO development, but no correlation with neuroimaging and spasticity (49). Citta-Pietrolungo et al. (50) defined that coma, immobility and spasticity were likely to be etiologic factors in HO development.

Spielman et al. (53), in their study, suggested that spasticity led to HO development in patients with TBI and reported that all of 20 TBI patients with spasticity developed HO. It has been reported that HO is seen along with spasticity in TBI patients, HO is regressed along with spasticity when neurological recovery occurs, and surgery increases the risk of relapse of HO. In a retrospective study performed on 496 patients with TBI, it was shown that spasticity was completely established in all of the patients who developed HO and 89% of the joints developed HO located in spastic extremity (31).

It is reported in the literature that HO incidence increased if elbow joint is also injured with TBI (51). In TBI patients with fractures, an excessive callus tissue is formed, but fracture union is delayed compared to those without TBI. Furthermore, it has been reported that the created callus tissue was not normal radiologically and histologically, including HO signs (52).

There are studies which reported that systemic infection is a probable risk factor for HO development in patients with TBI (39). Moreover, it is reported that HO can develop in patients requiring mechanical ventilation because of respiratory distress or in patients given iatrogenic neuromuscular blockage in intensive care units (54,55).

Conclusion

While etiology of NHO in patients with SCI and TBI is not clear yet, humoral, neural, immunological and local factors may play a role in the pathophysiology. Vascular stasis, oedema, tissue hypoxia, hypercalcemia, alterations in sympathetic nervous system activity, proprioceptive sensory deficit, prolonged immobilization and exercises after immobilization

are the factors responsible for the development of NHO. Furthermore, there are some distinct clinical factors contributing to the development of NHO in both diseases.

It is concluded that more comprehensive studies are needed to demonstrate the effects of the individual types of therapeutic exercise and the optimum timing in the prevention of NHO development in addition to detection and prevention of risk factors in order to contribute its therapy.

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