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Review

Neurogenic heterotopic ossification: A review. Part 1

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ABSTRACT

BACKGROUND: Heterotopic ossification is the formation of bone tissues in the soft tissues of the body. A distinct form of heterotopic ossification is neurogenic, that is, resulting from severe injury to the brain or spinal cord of different genesis. Neurogenic heterotopic ossification is a complex multifactorial process of differentiated bone formation in the paraarticular soft tissues of large joints. Heterotopic ossification leads to the formation of persistent contractures and ankylosis, which cause severe disability and complicate rehabilitation.

AIM: To analyze publications dealing with various aspects of neurogenic heterotopic ossification.

MATERIALS AND METHODS: In the first part of our review, we present the results of the literature analysis on the epidemiology, risk factors, pathogenesis, and clinic and laboratory diagnosis of neurogenic heterotopic ossification. Scientific literature databases PubMed, Google Scholar, Cochrane Library, Crossref, and eLibrary were searched for without language limitations.

RESULTS: Current literature data on heterotopic ossification in patients with central nervous system pathologies are presented. Topical questions of etiology, risk factors, pathogenesis, and clinic and laboratory diagnostics of this pathological process are highlighted.

CONCLUSIONS: Understanding the risk factors of heterotopic ossification development and their prevention in the context of the modern knowledge of heterotopic ossification pathogenesis may help reduce the incidence of heterotopic ossification in patients with severe central nervous system injury.

Keywords: neurogenic heterotopic ossification; heterotopic osteogenesis; spinal cord injury; cerebral trauma.

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Научный обзор

Нейрогенная гетеротопическая оссификация. Обзор литературы. Часть первая

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АННОТАЦИЯ

Обоснование. Гетеротопическая оссификация — это образование костной ткани в мягких тканях организма. Отдельной формой гетеротопической оссификации является нейрогенная, то есть возникающая в результате тяжелого повреждения головного или спинного мозга различного генеза. Нейрогенная гетеротопическая оссификация — сложный многофакторный процесс формирования дифференцированной кости в параартикулярных мягких тканях крупных суставах. Гетеротопическая оссификация приводит к формированию стойких контрактур и анкилозов, обусловливающих тяжелую инвалидизацию и затрудняющих реабилитацию этих пациентов.

Цель — проанализировать публикации по различным аспектам нейрогенной гетеротопической оссификации.

Материалы и методы. В первой части обзора представлен анализ литературы, посвященной эпидемиологии, факторам риска формирования, патогенеза, клинической картины и лабораторной диагностики нейрогенной гетеротопической оссификации. Поиск данных осуществляли в базах научной литературы PubMed, Google Scholar, Cochrane Library, Crossref, eLibrary без языковых ограничений. Глубина поиска составила 30 лет. В процессе написания статьи использовали метод анализа и синтеза информации.

Результаты. Изложены современные литературные данные по проблеме гетеротопической оссификации у пациентов с патологией центральной нервной системы. Освещены актуальные вопросы этиологии, факторов риска, патогенеза, клинической картины и лабораторной диагностики данного патологического процесса.

Заключение. Понимание факторов риска развития нейрогенной гетеротопической оссификации и их профилактика в контексте современных знаний о патогенезе этой патологии может способствовать снижению частоты формирования гетеротопической оссификации у пациентов с тяжелым повреждением центральной нервной системы.

Ключевые слова: нейрогенная гетеротопическая оссификация; гетеротопический остеогенез; травма спинного мозга; черепно-мозговая травма.

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BACKGROUND

Heterotopic ossification (HO) is a pathological formation of differentiated bone tissue outside the skeleton, that is, in places not related by continuity with the initially determined skeletogenous mesenchyme [1].

HO formation after injury was first described by Reidel in 1883. A more detailed description of HO can be found in the publications by Dejerne, Ceiller, and Dejerine-Klumpke, who studied HO formation during the First World War in soldiers with spinal cord injury (CSCI) [2].

HO can be either a clinical manifestation of hereditary diseases, such as fibrodysplasia ossificans progressiva, or an acquired condition resulting from injuries and burns [3]. HO has been reported to emerge during hematoma formation and in a primary tuberculosis focus, postoperative scars, foci of atherosclerotic calcification of large vessels and heart valves, tumors of various histogenesis, ligamentous apparatus of the spine, and other skeletal parts in the area of ligament attachment [4, 5]. A neurogenic HO (NHO) is a result of severe damage to the brain or spinal cord of various causes such as severe traumatic brain injury (TBI), CSCI, cerebral stroke, and cerebral anoxia [6].

This study aimed to analyze publications on various aspects of NHO.

MATERIALS AND METHODS

Part 1 of this review presents the results of an analysis of the literature on the epidemiology, risk factors for HO formation, pathogenesis, clinical presentation, and laboratory diagnostics of NHO. A data search was performed in the scientific literature databases of PubMed, Google Scholar, Cochrane Library, Crossref, and eLibrary without language restrictions for a search depth of 30 years. Then, the obtained information was analyzed and synthesized.

RESULTS AND DISCUSSION

Epidemiology and risk factors

NHO occurs in 10%–23% of patients with severe TBI, 10%–53% of patients with spinal cord injury [7, 8], and up to 65% of the patients who had blast injuries [9, 10]. According to Reznik et al., who analyzed the treatment outcomes of 413 patients (TBI, $n = 262$; CSCI, $n = 151$), NHO occurs more often after CSCI than after TBI, as NHO was diagnosed in 3.9% of patients with severe TBI and 10.6% of patients with CSCI [11].

The literature presents extremely contradictory positions on the sex-related incidence of NHO, that is, 2.5 times in men [12, 13] and 4 times in women [14]. According to an experimental modeling of HO in mice, 30% more ectopic bone was formed in male than in female mice, and the authors attributed this to increased levels of insulin-like growth factor-1 and bone morphogenetic protein (BMP) in male mice [15].

Data on the age-related incidence of NHOs in the world literature are more homogeneous than sex data. NHO is more often detected at the age of 20–30 years; however, this pathology develops less frequently in children than in adults, mainly at the age of ⩾10 years [7, 16, 17]. The earliest detection of NHO was described in a 5-year-old child [16]. In pediatric patients, no clear correlations were found between the incidence of NHO and sex [16, 17].

According to Estraneo et al., who retrospectively analyzed the examination findings and treatment outcomes of 278 patients with brain damage of various etiologies, NHO occurs more often in patients with TBI (19.3%) than in patients with anoxic (10.7%) and vascular (6.4%) brain damage [13]. Among patients with TBI, NHO was more often recorded in patients with diffuse axonal injuries [14]. NHO was noted two times more often in patients in a vegetative state following TBI than in patients with a short-term impairment of consciousness [17].

Citak et al. believed that complete dissection of the spinal cord is the main predisposing factor in NHO formation in patients with CSCI [18]. The location of spinal cord injury also affects the incidence of NHO formation; as with damage at the cervical and thoracic levels, the NHO risk is higher than with damage at the lumbar level [19].

In addition to the direct finding of spinal cord or brain injury, additional risk factors for NHO development have been identified, namely, chest trauma, tracheostomy, nicotine use, pneumonia, and urinary tract infection [18, 20].

According to many authors [13, 15, 18], artificial lung ventilation is also a risk factor for NHO formation after both TBI and CSCI. This is due to the development of respiratory alkalosis resulting from prolonged artificial lung ventilation in some cases, and this contributes to NHO formation [21].

Krauss et al. considered hypercoagulable states as another risk factor for NHO occurrence in patients with CSCI complications [22]. This theory is consistent with that proposed by Reznik et al., who included deep vein thrombosis in the group of additional risk factors for NHO in patients with TBI and CSCI complications [11]. However, Yolcu et al. cited data from their meta-analysis and systematic review of the literature on risk factors for NHO development and declared the absence of a correlation between deep vein thrombosis and NHO risk in patients with CSCI complications [20].

According to Rawat et al., bedsores induce a local inflammatory process, which may be a trigger for NHO formation in patients with CSCI complications [23]. However, some authors believe that NHOs develop not in all patients with CSCI-related bedsores [18, 24].

Authors also have different and ambiguous positions regarding muscle spasticity as a risk factor for NHO. Some

authors still consider spasticity a risk factor [19, 20], whereas others do not agree with this [2]. Spasticity is registered in most patients with cerebral palsy; however, in modern international and Russian literature, NHO development in patients who have not undergone surgery or who have no history of trauma has not been mentioned.

The role of immobilization as a risk factor for NHO is still being studied [25–27], although Orchard et al. noted that the duration of bed rest was the only risk factor that was significantly associated with NHO formation [26]. These data can be interpreted as a direct relationship between the lack of movement and NHO formation; however, the period of bed rest depends on other factors in the NHO formation, such as the severity of damage to the brain and spinal cord and bone and soft tissue injuries. Moreover, the duration of bed rest increases the risk of bedsores and contributes to the development of a chronic inflammatory process. Thus, it is currently not possible to associate unambiguously the absence of movements and NHO formation.

Pathogenesis

Currently, NHO is believed to be formed by endochondral ossification, although some authors suggest that HO is formed by intramembranous ossification [3, 28]. In a study of 90 histological preparations from 18 patients with HO of neurogenic and nonneurogenic etiology, Foley et al. revealed that HO is formed by endochondral ossification and described six successive stages of HO formation, namely, perivascular lymphocytic infiltration, lymphocyte migration into soft tissues, reactive fibroproliferation, neoangiogenesis stage, cartilage formation, and enchondral bone formation. According to the authors, they cannot completely exclude the possibility of HO occurrence by intramembranous ossification; however, this probability is extremely low, given the lack of data on intramembranous ossification in all histological preparations [29].

The time required for callus formation and complete consolidation during fractures is significantly shorter in patients with concomitant injury of the central nervous system than in patients without neurological pathology. This finding was confirmed in experimental and clinical studies [30, 31]. Severe TBI and CSCI cause damage to the neurons, glia, and vasculature, thereby triggering a complex cascade of cellular and molecular changes that can contribute to further damage later from the time of injury. In such traumas, common mechanisms of secondary injuries may include excitotoxicity (damage and death of nerve cells by neurotransmitters that can hyperactivate NMDA and AMPA receptors), ion imbalance, oxidative stress, ischemia, edema, and neuroinflammation (the intrinsic immune system of the brain is activated by ischemia, injury, infection, and other factors, which is mediated by the secretion of cytokines, chemokines produced by the glia of the central nervous system, and endothelial and peripheral immune cells) [32]. Neuroinflammation causes damage to the blood–brain, blood–spinal, and blood–neural barriers [33] and creates conditions for the abnormal circulation of neuropeptides, particularly substance P and calcitonin gene-related peptides, which cause vasodilation, increase vascular permeability, and create conditions for the peripheral migration of inflammatory mediators and growth factors, potentially stimulating NHO formation [32–34]. Gautschi et al. confirmed this hypothesis in a laboratory. In vitro studies have shown that the presence of serum and cerebrospinal fluid in patients with TBI increases osteoblast proliferation [35].

Genêt et al. demonstrated the importance of the immunoinflammatory response as a necessary factor for NHO and revealed through their experiment that transection alone of the spinal cord does not lead to NHO in mice. The authors hypothesized that NHO development requires concomitant muscle tissue injury, which was modeled using the generally accepted muscle injury and repair model. The experiment was repeated on different genetic mouse strains, and similar results were obtained. As confirmed, this is not a genetically predisposed phenomenon [36], and damage to both the central nervous system and soft tissues is significant in NHO development [34, 37]. This finding correlates with data on the high incidence of NHO after mine blast injuries, causing severe damage to the brain and spinal cord and soft tissues of the extremities [38].

However, NHOs are formed in patients with stroke complications who do not have a history of soft tissue injuries [39]. According to Alexander et al., in patients with damage to the central nervous system, infectious and inflammatory processes (urinary tract infections, bedsores, tracheostomy, and pneumonia), which are considered risk factors for NHO development, are a trigger for cytokine production and immune system activation, which provides the basis for HO formation [37]. According to some authors, systemic inflammation and cytokine storm can initiate HO development in patients with severe COVID-19 [40, 41].

The release of cytokines and growth factors, including interleukin-1β, interleukin-6, oncostatin M, neurotrophin-3, activin A, bone morphogenetic proteins, transforming growth factor β, and others, from lymphocytes, macrophages, and mast cells initiates the differentiation of cells involved in NHO formation [3, 42]. The predominant source of cells that form HO are local stromal/fibroblastic cells of mesenchymal origin in the connective tissue of skeletal muscles and fascia and circulating stem and progenitor cells [1, 3].

Peripheral nerves are also sources of cells that are involved in NHO formation [33]. The expression of osteoblast-specific transcription factors has been identified in cells obtained from the peri- and endoneurium following HO induction [43]. When the integrity of the blood–neural

barrier is disrupted, these cells migrate from the endo- and perineural areas of the peripheral nerves to the area where HO is developing and further differentiate into osteoblasts, chondrocytes, and brown adipocytes [44].

Cells from experimental animals, which may be involved in HO formation, were identified based on the expression of TIE2, PDGFRα, SCA1, GLAST, FSP1, STRO1, GLI1, and MX1. However, in humans, these cell types have not yet been accurately described. Other cell types may be responsible for HO development in humans [45]. For example, researchers do not have a consensus regarding the participation of endothelial cells in NHO formation. According to Medici et al., the expression of active ALK2 in endothelial cells causes endothelial–mesenchymal transition and the acquisition of a stem cell-like phenotype, which leads to the cell becoming capable of osteogenic differentiation [46]. However, further studies did not confirm the involvement of endothelial cells in NHO formation, although their contribution to HO formation was confirmed in an experimental burn and traumatic model [47].

Numerous studies have indicated the involvement of various signaling pathways, such as BMP/SMAD and WNT/β-catenin, in HO regulation [24, 27, 48].

BMPs are members of the transforming growth factor beta (TGFβ) superfamily. Canonical TGFβ/BMP signaling represents a linear cascade involving TGFβ/BMP ligands, two types of receptors (types I and II), and signal transducers (SMADs). The binding of the receptor to BMP leads to signal transduction through the SMAD 1/5/8 pathway and to TGFβ to the phosphorylation of SMAD2/3. Activated SMADs bind to SMAD4, and the complex then accumulates in the nucleus, where it regulates the target gene expression. One of the downstream targets of these pathways is the gene encoding RUNX2, a well-known master regulator of osteogenesis, which is also aberrantly expressed in ossified soft tissues [49, 50]. The TGFβ-dependent activation of SMAD2/3 promotes osteoprogenitor migration and differentiation at early stages while suppressing further stages of osteogenesis. The TGFβ-dependent pathway, which does not involve SMAD, can lead to the activation of the p38 MAPK or ERK1/2 MAPK pathways through the TAB1–TAK1 complex, which induces RUNX2 activation and promotes osteoclast differentiation [51]. BMPs and TGFβ can activate the SMAD-independent pathway. Most BMP ligands are potent osteogenic agents, acting through both SMAD-dependent and SMAD-independent signaling pathways that induce osteogenic transcription factors [52, 53].

The TGFβ-dependent activation of SMAD2/3 promotes the migration of osteogenesis precursor cells and their differentiation at early stages but also inhibits osteogenesis at further stages [54]. The TGFβ/BMP signaling interacts with other pathways during embryonic and postnatal development. For example, the crosstalk between the canonical WNT pathway, TLR pathway, or mTOR pathway has been described. Notably, mTOR modulates hypoxia and inflammation signaling in the early stages of HO, and in later stages, the same pathway is critical for chondrogenesis and osteogenesis [52]. Increased mTOR pathway signaling was demonstrated using a mouse model of fibrodysplasia ossificans progressiva [55].

The hypoxic environment stabilizes hypoxia-inducible factor 1α (HIF1α), which regulates the production of many proteins, such as vascular endothelial growth factor or BMP, which are involved in HO formation [42]. The analysis of three different mouse models of fibrodysplasia ossificans demonstrated increased HIF1α signaling under hypoxic conditions [56]. HIF1α expression was also increased in adipose tissue samples obtained from patients with severe burns [56, 57].

However, the mechanisms underlying HO development in noncarriers of any mutations are still unclear. Moreover, even in patients with fibrodysplasia ossificans progressiva, soft tissue HOs are not always consistently noted and appear to result from traumatic injury and the body's inflammatory response, strongly suggesting a link between the immunoinflammatory response and HO.

Thus, in vivo experimental studies have shown that the transplantation of bacteria into the tibia of an experimental animal increases the callus volume. In the same study, lipoteichoic acid (LTA), a TLR2 activator derived from the bacterial cell wall, was identified as an osteostimulating factor [58].

Data from these studies suggest that the underlying mechanism of HO formation is related to TGFβ/BMP pathway signaling, which leads to the expression of osteogenic transcription factors. Damaged tissue factors cause the activation of the mTOR, WNT, or TLR pathway, which can either interact with TGFβ/BMP or act independently, namely, promote the expression of osteogenic factors and induce HO formation [27].

Clinical presentation

NHOs are formed para-articularly to the hip (60.9%), knee (14.3%), elbow (21.3%), and shoulder (35%) joints, limiting the range of motion of the affected joint, up to complete ankylosis, leading to severe pain and compression of nerves and blood vessels [8, 59].

We have not found a single case description of intra-articular NHOs. Therefore, NHO is always extra-articular. The joint capsule is also always preserved. The tendon attachment sites can serve as landmarks during clinical and instrumental examinations. The veins are compressed, whereas the diameter of the periarticular arteries is usually not altered. Certain patients may experience bursitis of the affected joint as a response to damage to the periarticular tissues in HO development [2].

In patients with CSCI, NHO is usually detected caudal to the level of the spinal cord injury, and the hip joints are most often affected. According to Garland et al., damage to the hip joints in these patients accounts for up to 97% of all clinically significant NHOs [7].

Severe TBI results in generalized HO involving the periarticular structures of the hip, knee, elbow, or shoulder joint [60]. In 40% of such patients, only one joint is involved in the pathological process [28]. In more than two-thirds of cases, NHOs are located in the periarticular tissues of the hip joint or soft tissues surrounding the femur. In approximately 90% of patients with TBI and associated intra-articular fractures or elbow dislocation, Hos develop in the area of the injured joint, whereas the incidence of clinically significant HO of the elbow joint in patients without severe TBI ranges from 3% to 6% [14].

According to Ebinger et al., the etiology of NHO can influence its localization in relation to the hip joint, that is, in 55% of severe CSCI, NHO is located on the anterior surface of the thigh, and in 40% of patients with cerebral stroke or TBI, it is located on the anteromedial surface. The NHO located on the posterior surface of the thigh was noted in 32% of patients with complications of severe cerebral hypoxia [61]. Ko believed that with CSCI complications, hip-joint NHOs are more often located postero- and anteromedially, and this is associated with the static nature of the adductor muscles of the thigh [62]. Garland had the same arguments, describing NHO formation predominantly in the posteromedial parts of the hip joint in patients with complications of severe TBI [7]. Quite often, NHOs are located between the anterior superior iliac spine and the femur [61].

NHOs rarely extremely occur in the ankle and radiocarpal joints, as well as in the small joints of the hands and feet [6, 7].

Regarding the timing of NHO formation, most often, they develop between weeks 3 and 12 after CSCI [8]. According to Wittenberg et al., the period at the greatest risk for NHO occurrence is 5 months after CSCI [63]. The clinical presentation depends on the disease phase, of which there are four, namely, acute, subacute, chronic immature, and chronic mature HO [64].

In the acute phase (approximately 2 weeks), dense, often hyperemic edema is detected in the area of HO formation. Edema is located around the joints and can significantly limit movement in them. In this phase, the clinical presentation resembles thrombosis of the veins of the lower extremities, which leads to frequent diagnostic errors, particularly if it is impossible to conduct ultrasound diagnostics of blood vessels and doctors are unaware of other possible causes of these symptoms [65]. The onset of the clinical manifestations of NHO in patients with CSCI may not be accompanied by subjective sensations because of sensory deficits characteristic of this type of injury. These patients experience increased body temperature and muscle spasticity. If the NHO is small, then its formation would not be accompanied by local reactions, such as hyperemia, local temperature increase, and edema. HOs of this size rarely induce contractures in the joints of the limbs and, therefore, do not impair the quality of life [15].

In the subacute phase (2–8 weeks), signs of the local inflammatory process regress, and affected joints had limited movements [8]. HOs occur in soft tissues, expand, and fuse with the periosteum of adjacent bone structures [2].

In the chronic phase of immature HO (6–8 months), dense, irregularly shaped masses are palpated in the affected joint site, and the joint range of motion decreases [3].

The maturation of bone tissue ossification is completed within 6–18 months. Mature HOs resemble normal bone tissues both histologically and radiographically and consist of tubular bone with Haversian canals, cortical layer, blood vessels, and bone marrow with some level of hematopoiesis [45].

In the chronic phase of mature HO (8–18 months), joint ankylosis can occur. Pathological formations palpated in the affected joint are already characterized by bone density [15]. Some authors note that joint ankylosis is formed in the immature HO phase [28, 61].

Laboratory diagnostics

Nonspecific markers of inflammation, such as C-reactive protein, can be used to monitor disease activity, as normalization of C-reactive protein levels correlates with the resolution of the inflammatory phase of HO [62]. According to Wilkinson and Stockley, a rise in body temperature in combination with increased C-reactive protein levels and creatine kinase activity should be regarded as HO signs [66].

Alkaline phosphatase (ALP) is a sensitive but nonspecific indicator of HO. During HO formation, the ALP level increases significantly. However, as soon as the growth of ossification stops, the enzyme level decreases and returns to normal; therefore, it cannot be used for diagnosing HO [67]. ALP levels begin to increase within an average of 7 weeks before the emergence of the first clinical signs of HO and reach a peak within 3 weeks before clinical manifestations occur. From this time on, the ALP level decreases gradually and reaches normal levels within approximately 5 months. The degree of increase in ALP levels depends directly on the HO size. Massive bone formation can lead to a long-term increase in ALP levels, whereas minor HO may not be accompanied by its changes [28]. According to Kluger, ALP levels did not increase in most pediatric patients [16]. Thus, the normalization of the ALP level does not indicate the stabilization and cessation of the NHO growth. However, nowadays, the measurement of ALP levels is the only widely available method in the differential diagnostics of early NHO with other

inflammatory processes because this indicator increases noticeably during the active growth of NHO and does not change significantly during inflammation [67].

Prospects for laboratory diagnostics

The dysregulation of microRNAs may be significant in HO development. For example, decreased levels of microRNA-421 in patients with humeral fractures are associated with the overexpression of BMP2 and a higher incidence of HO [68]. In the future, changes in microRNA levels can be considered possible indicators of NHO development.

HO formation is characterized by a significant increase in bone tissue formation compared with those in practically healthy individuals and patients with CSCI without NHO. Edsberg et al. conducted a comparative analysis of the proteomic profile of the blood serum of patients with HO of nongenetic etiology and patients without HO (control group, after total hip replacement), which established that the production of the preproprotein osteocalcin, a precursor of osteomodulin and the preprotein of isoform 2 chain of alpha-1 (v) collagen, increased statistically significantly in the HO group. These proteins can be considered potential clinical biomarkers of HO [69]. Povoroznyuk et al. believed that an osteocalcin level of ⩾49.6 ng/mL and N-terminal propeptide of type 1 procollagen level of ⩾187.3 ng/mL should be considered NHO markers in patients with CSCI complications, and these markers can be included in the diagnostic algorithm [67]. Further study of the markers of bone tissue remodeling will allow for early diagnostics, outcome prediction and, possibly, NHO prevention.

CONCLUSION

NHO is a complex multifactorial process of bone formation in the para-articular soft tissues of large joints, causes severe disability, and complicates the rehabilitation of patients with complications of central nervous system damage. In the context of modern knowledge about the pathogenesis of NHO and monitoring bone tissue remodeling, understanding the risk factors for NHO development and their prevention can help reduce the incidence of HO in patients with complications of severe central nervous system damage.

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All authors made significant contributions to the study and preparation of the article, and they read and approved the final version before its publication.

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