Review Article

Heterotopic Ossification: Prevalence and Clinical Characteristics in Spinal Cord Injured Patients Treated at CIREN

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ABSTRACT

Introduction: Neurogenic heterotopic ossification is the abnormal formation of bone in soft tissues or muscles that occurs after a neurological injury, its cause is still unknown. In the spinal cord injured patient, it has a variable prevalence, which is not known in our country and some relevant aspect of treatment.

Objective: To define the prevalence of heterotopic ossification in the spinal cord injured patient, to study the clinical characteristics and possible associated risk factors, and diagnosis.

Method: A descriptive and retrospective study was carried out in a period of 3 years in patients with traumatic spinal cord injuries who are undergoing a neurological restoration program at the International Center for Neurological Restoration, to which a clinical-neurological evaluation, imaging studies in search of abnormal periarticular calcifications, as well as studies of markers of bone activity and inflammation. In patients with such calcifications, the Brooker classification was performed to assess its severity.

Results: Of 136 patients studied, 6 had calcifications in periarticular soft tissues, 5 male and one female, 3 cervical injuries and 3 dorsal injuries; the history of severe trauma associated with spinal surgery, ventilatory complications, and infections are the risk factors found. All calcifications are in the maturation phase, causing severe joint involvement in 2.94% of patients.

Conclusions: Neurogenic heterotopic ossification in patients with spinal cord injury has a prevalence of 4.41%. Conservative treatments carried out in this phase are unable to improve the degree of joint mobility.

INTRODUCTION

Neurogenic Heterotopic Ossification (NHO) is the abnormal formation of bone in soft tissues or muscles around a paralyzed joint, secondary to neurological involvement, the pathogenesis of this process is still not well understood and can range from a non-significant radiological finding to a clinically significant and disabling situation. There are different etiologies, the one of genetic origin with an autosomal dominant inheritance and that has two clinical forms, Fibrodysplasia ossificans progressive and progressive bone heteroplasia [1,2]. Heterotopic Ossification (HO) secondary to trauma, fractures, burns, postoperative, and associated with spondyloarthropathies, do not have a well-defined pathogenesis and are associated with other risk factors.

The third group is of neurogenic origin, first described in 1918 by Dejerine and Ceilier, in a spinal cord injured patient during World War I, introducing the term paraosteoarthropathy, although other names such as myositis ossificans have been suggested and heterotopic ossification. It presents as a consequence of closed head trauma, coma, cerebrovascular disease, spinal cord injury, motor neuron or peripheral nerve diseases [3-5]. The incidence of HO in spinal cord injured patients varies between 10-53%, becoming clinically significant in 20-30% of cases, producing joint ankylosis in 3-5% of patients. It occurs below the level of injury, frequently affecting the hip joint, followed by the knee, being the period of greatest risk in the acute phase of the injury between 3 and 12 weeks, it is more frequent in complete spinal injuries, affecting more men than women, between 20 and 30 years of age [6,7].

Multiple factors have been involved in the pathogenesis of NHO, such as trauma, hypercalcemia, tissue hypoxia, changes in sympathetic nerve activity, prolonged immobilization or paralysis, muscle spasms, severe bleeding, inflammation, urinary infection, natural response to trauma, pressure ulcer, imbalance of paratorhomone and calcitonin among others, however attempts to understand how local or systemic factors act in the production of calcifications have failed [5]. Three conditions are necessary for OH to occur: the presence of osteogenic precursor cells, inducing agents or signaling pathways, and a permissive environment. The demineralized bone matrix could invoke bone formation ectopically and a Bone Morphogenetic Protein (BMP) a causal agent, associated with traumatic ischemic muscle degeneration, facilitates the tissue expression of said protein in interaction with other cellular and soluble elements. This protein is apparently capable of changing the development of mesenchymal cells in muscle to bone, when respiratory and nutritional requirements are also met [5,8,9].

Other proposed non-exclusive mechanisms involve concomitant injury to the central and peripheral nervous system associated with trauma, as an initial factor in the inflammatory cascade, the creation of the hypoxic environment around muscles and joints, the release of angiogenic factors, the deposition of fibroblasts and collagen, which lead to the formation of mesenchymal and osteoprogenitor cells with osteoblastic activation in this microenvironment [10,11].

The clinical diagnosis is made by symptoms and signs, although they are not specific, patients may present joint and muscle pain, increased volume of the affected region, limitation in joint mobility, accompanied by fever, although patients with Spinal Cord Injury (SCI) may not experience pain. Increased biological markers such as leukocyte Alkaline Phosphatase (ALP), creatine phosphokinase, C-Reactive Protein (RPc), prostaglandin E2, and Erythrocyte Sedimentation Rate (ESR) have been associated with HO after SCI, although they are not specific; diagnosis is made in the early phase with the triple phase bone scan, which demonstrates increased absorption of osteotropic radio nucleotides [12,13]. The main objective of the present work was to define the prevalence of heterotopic ossification in the spinal cord injured patient, to study the clinical characteristics and possible associated risk factors and diagnosis.

MATERIAL AND METHOD

A retrospective descriptive study was carried out, for which we reviewed the medical records of 406 patients discharged from the CIREN Spinal Cord Injury Clinic in the period 2016-2018, of which 136 had a history of traumatic spinal cord injury. Demographic variables such as age and sex, clinical variables: level of injury, time of evolution of the same, history of surgery, comorbidities associated with spinal trauma were taken into account as possible associated factors: mechanical ventilation, acute infections, pressure ulcer, excluding patients with non-traumatic spinal cord injuries. These patients underwent a clinical evaluation that included the osteomyoarticular system, in addition to plain radiographs, CT or MRI of the involved spinal segment, in addition to the joint with positive findings on physical examination, depending on the type of injury, presence of osteosynthesis material, as well as hematological studies with alkaline phosphatase, C-reactive protein and Erythrocyte Sedimentation Rate (ESR). The extent of calcification was classified according to Brooker's criteria [14]. The results are presented with frequency variables.

RESULTS

136 patients met the inclusion criteria, 102 male and 34 female, with different times of evolution of the injury, from 6 months to 10 years, in relation to the location of the level of injury, three cervical and three thoracic, all presented complete

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spinal cord injury with Asia A as well as a grade I-II Ashworth scale spasticity classification. In relation to sex, the male: female ratio was 5 to 1, similar to other reports, which is also related to the incidence of traumatic spinal cord injuries, which is higher in the male population. Regarding the etiology of the trauma, Gunshot Wounds (GW) were the cause of spinal cord injury in three of the patients, followed by a car accident in two and a sports accident in one.

Table 1: General and clinical data of the series of patients.

General data and diagnosis	Clinical and neurological history	Clinical and imaging findings
No.1.Age 49 years, male, Diag Quadriplegia post-traumatic level C5-C7 due to sports accident	Pressure ulcer, Respiratory failure (tracheostomy), Spine cord surgery. Urinary tractinfection.	ESR normal, ALP 371, Bony pelvis X-ray: heterotopic calcifications of the femoral head, trochanter and acetabular eyebrow. Brooker 4
No.2. 34 years old, male, quadriplegia post-traumatic level C7-T1 by GW	Loss of consciousness, respiratory failure, mechanical ventilation, tracheostomy, hemopneumothorax, Peritonitis, Pressure ulcer, Urinary tract infection	ESR Normal, normal ALP, IMR with myositis ossificans from the ilium to the upper third of the left leg, femoral head calcifications Brooker 4
No 3 Age 19 years, male T7-T8 level post-traumatic esp paraplegia, car accident	Hemopneumothorax, spine surgery (2), Urinary tract infection	ESR normal, bone pelvic X-ray: heterotopic calcifications and bone excresence of the left femur. Brooker 2
No. 4. Age 21, male, Diag. ParaplegiaPost-traumatic level T9-T10, GW	Pressure ulcer. Urinary tract infection	ESR normal, normal ALP, bone pelvic X-ray: bone excretions in both knees Brooker 1
No 5.37 years, Female Quadriplegia.Post-traumatic level C6-C7 automobile accident	Spine surgery, Pressure ulcer, Urinary tract infection. anemia	ESR 42 mm/h, normal ALP, positive RPc, HB 10 g / l Bone pelvic x-ray with heterotopic calcifications in both hips Brooker 3
No 6.38 years, male Paraplegia.post-traumatic level D4-D5 by GW	Hemopneumothorax, Pressure ulcer Urinary tract infection. Anemia, gallstones	ESR normal, ALPnormal.MRI with deformity of both hip joints, bony excretions, soft tissue myositis ossificans, marked reactive osteosclerosis in hip joints Brooker 4

The presence of calcifications in periarticular soft tissues was diagnosed in six patients (Table 1), describing hip joint involvement in 4 patients, with variable degrees of joint mobility compromise, and knee involvement in 2 patients, without significant compromise of joint mobility, reporting a general prevalence of 4.41%. A history of spinal surgery was reported in four of six patients and according to the level of spinal cord injury and the sequelae of the trauma, three patients had cervical involvement, with sequelae quadriplegia and three had paraplegia due to dorsal involvement, both locations were associated with more severe joint involvement (Brooker 3 and 4), no patients with lumbar involvement and heterotopic ossification were reported.

Other antecedents that are described as associated factors are respiratory complications and infections, in four of six patients (66.6%) as well as a co-morbidity reported especially in the early stages of spinal cord injury, Pressure Ulcer (PU) in five of six patients for 83.3%. The hip joint with unilateral or bilateral ankylosis and the knee were the most frequent locations of calcifications; all in the maturation phase, since it is in the phase of clinical and neurological stability that they are incorporated into the intensive rehabilitation program. The etiology of trauma reported in decreasing order, firearm injuries (3), car accident (2), and sports accident (1).

In relation to the biochemical markers performed, one patient had elevated levels of ALP (16.6%), in the rest this parameter was normal; it is a biomarker of bone activity, which tends to normalize after 12 weeks and all patients had more than 24 months of evolution. Acute phase reactants such as erythrocyte sedimentation rate and C-reactive protein were positive in one of six patients, both related to an upper urinary tract infections process. Four patients were evaluated with plain bone pelvis radiography, due to having osteosynthesis with non-biocompatible material, and in two patients an MRI was performed, finding that the hip joint was the most affected in 4 of 6 patients, being described from the imaging point of view

the presence of abnormal calcifications in the femoral head, with joint space deformity, myositis ossificans, bone excretions in the femur or knees, all lesions compatible with the diagnosis of OH.

In relation to the severity of the lesions, four out of six patients presented significant compromise of joint mobility (Brooker between 3 and 4) with different degrees of joint ankylosis, with bone bridges, and isolated calcifications were found in two patients, which did not compromise joint mobility, with the hip generally being the most affected joint in five out of six patients.

DISCUSSION

The prevalence of HO found in this series has been 4.41%, it is considered low if we compare it with other reports, in which it varies between 20-30%, despite the most severe forms, they present with a frequency between 3 -5% and in this series 4 of 6 patients had involvement that reached the degree of joint ankylosis, for 2.94%, a value very similar to the figure reported [6,15].

The prevalence of OHN is highly variable depending on the time of evolution where the report is made, being higher in rehabilitation centers, influencing the presence of clinical symptoms associated with pain and functional limitation, with under-records above all in patients with SCI in the acute phase; In this report, the time of evolution of the spinal cord injury and the diagnosis of calcification has been between 2 and 5 years, although the date of the appearance of calcification is unknown, however its appearance has been reported up to 20 years later of a spinal cord injury [16], being able to increase this prevalence in prospective studies. In the factors associated with spinal cord trauma and neurological sequelae, they were found: spinal surgery, respiratory complications, systemic or localized infections and pressure ulcers. The latter has been correlated with NHO in different studies, together with spasticity and the time elapsed since the injury as factors that are independently associated with HO [17]. The truth is that the association of calcifications with multiple PUs is due to infections deep enough close to the bone, which are accompanied by tissue hypoxia, prolonged immobilization and an inflammatory response; however more basic and clinical research is required to confirm this relationship [18].

Regarding respiratory failure with or without hemopneumothorax, as a reported antecedent in four patients, we can infer a possible association, taking into account recent evidence, which suggests that hypoxia is crucial in the pathogenesis of HO , in which hypoxia-inducible factor α1 acts as the main regulator for the expression of tissue receptors, stimulating vascularization, together with pro-inflammatory cytokines and biomechanical factors, promoting angiogenesis, chondrogenesis and cell differentiation [8,19,20]. Another non-exclusive mechanism of this pathogenic hypothesis has proposed that the relationship between the homeostatic balance of calcium, oxygen and the pH level altered by artificial ventilation, which generates a respiratory alkalosis in the acute phase, may contribute to accelerated formation of ectopic bone [21]. When we relate the etiology of trauma as a possible risk factor in NHO, we observed that three of the six patients in the study had gunshot wound as the cause (50%). In this sense, the epidemiological and clinical characteristics of HO have been studied in patients with lesions caused by GW, explosives and similar, describing up to 68% of association, even in the absence of neurological lesion, being explained by a local and systemic inflammatory response as a possible pathogenic mechanism [22-24].

The biomarkers of bone activity tend to normalize after 12 weeks of the appearance of calcification, the patients in this series had more than 24 months of evolution, which explains the presence of normality of the leukocyte Alkaline Phosphatase (ALP)in five of the patients, one patient presented increase in the enzyme, which could be due to other causes, taking into account its multiple tissue origins and the use of various drugs, including antispastic and antineuritics, which can increase it. In relation to the acute phase reactants: erythrocyte sedimentation rate and C-reactive protein are positive in one of six patients, both explained by a symptomatic infectious process of the upper urinary tract, a frequent comorbidity in this population. Other acute phase markers such as prostaglandin E2 and D-dimer, although they have a significant predictive value for OH, still need validation and were not evaluated in this study [21,25].

Imaging studies such as triple-phase CT or magnetic resonance imaging are very useful tools for early-stage diagnosis, as well as allowing classification of lesions and better visualization of

heterotopic bone, vascular compromise, and bone bridge discontinuity for better planning when considering surgery. Plain radiography in anteroposterior view of the bony pelvis, although less sensitive, constitutes a specific, inexpensive and feasible study for patients with metal fixations, projectile remains or other contraindications to magnetic resonance imaging; it becomes positive 2 to 6 weeks after the appearance of HO, and allows patients to be evaluated when the lesion is mature, as in this series [26].

The radiography of four patients showed positive findings, being useful in the diagnosis and classification of the degree of compromise of joint mobility, in two patients an MRI was performed, which shows abnormal calcifications and allows a better visualization of the heterotopic bone, the compromise of neighboring structures, visualize the different degrees of ankylosis and bone bridges, classifying with Brooker between 3 and 4, with the hip being the most affected joint, a behavior similar to other reports [27].

Although useful and easy to apply, adjustments have been proposed to the Brooker classification, since it does not allow to determine risks for surgery and is pessimistic in relation to the recovery of joint mobility in grades 3 and 4, suggesting the Mavrogenis classifications and Arduini, which are focused on the anatomical location of ossification: anterior, posterior, anteromedial or circumferential, estimate the blood loss when the surgery is performed, as well as the possibility of recurrence after surgery and the prognosis. However these approaches have not yet been validated and require further investigation from a clinical point of view [28-30].

More recently it has been used and validated both in animals and humans Raman spectroscopy, to detect injuries as early as 16 days after the trauma, which allows studying the early development of the process. It must be differentiated from other clinical entities such as deep vein thrombosis, osteomyelitis, cellulitis and bone tumors, with ultrasound being useful and specific to rule out these processes and even to follow the maturation of OH, with good sensitivity but little specificity [31]. In relation to the neuro-restorative treatment program carried out, it consisted of intensive, comprehensive and personalized physical rehabilitation according to the sequelae and complications of the spinal cord injury, it included pharmacological modulation of spasticity in all patients, non-steroidal anti-inflammatory drugs in two patients due to chronic pain, use of sodium etidronate in two patients due to osteoporosis, biophysical agents with magnetic fields were applied in all, gentle physical therapy in the area of calcification to improve muscle tone and trophism, increase joint width and improve posture, in addition to the rest of the kinesiology program according to the objectives set for each patient. No other interventions such as radiotherapy or surgeries were performed. Qualitative improvement is reported in all patients, without evidence of significant changes in joint width, although this is a small series that does not allow other inferences, recommending subsequent follow-up by the Orthopedic specialty to evaluate possible surgical resection in three patients.

CONCLUSIONS

NHO is a complication that occurs in patients with spinal cord injury of traumatic etiology, with a low prevalence in this series. Multiple factors have been related; among the most common are the severity of spinal trauma and surgery, ventilatory compromise in the acute phase, and a history of other morbidities such as infections and pressure ulcers. The conservative treatments available do not manage to improve joint mobility once the calcification maturation phase has reached, making it necessary to standardize the different therapeutic options in healthcare protocols, for diagnosis in earlier phases and multidisciplinary therapeutic management in the spinal cord injured patient.

RECOMMENDATIONS

Clinical research constitutes the way to search for possible effective therapeutic targets in the prevention of NHO, once the cellular and molecular pathophysiological mechanisms are better understood. Fortunately, there are promising avenues for research in the identification of these as well as in the study of prognostic biomarkers and prophylactic therapies that are suitable for patients with complex trauma with CNS lesions.

CONFLICTS OF INTEREST

There are no conflicts of interest for the authors of this manuscript.

All patients and family members signed the informed consent, as they were included in the neurological restoration program, which is on file in the clinical history

Contribution of the authors was the same in the realization and presentation of the study and presentation of the manuscript for publication.

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