Protocol Proposal for Management of Neurogenic Heterotopic Ossification in Spinal Cord Injury: A Rehabilitation Center Experience

Proposta de Protocolo para o Tratamento da Ossificação Heterotópica Neurogénica em Lesão Medular: A Experiência de um Centro de Reabilitação

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Abstract

Introduction: *Neurogenic heterotopic ossification (NHO) is a frequent complication of spinal cord injury (SCI). NHO poses a diagnostic challenge and can compromise patient functionality. Our aim is to characterize a case series of NHO in SCI patients, from a rehabilitation center, review the literature and propose a management protocol.*

Methods: *A small case series is described based on medical records. A review of the literature for etiology, diagnosis and treatment of NHO in SCI was performed.*

Results: *A total of 5 SCI patients were included, 3 were male (median age 48.4 years). Three were traumatic SCI, 2 had concomitant traumatic brain injury (TBI), all were thoracic lesions (T4-T9), 4 were complete lesions, 3 had autonomic dysreflexia. Median time from SCI to NHO was 2.1 months. All presented with swelling around the hip. Alkaline phosphatase (AP) and c-reactive protein (CRP) rises were documented.*

Main Protocol steps:

- *Calcium, phosphorus, AP, CK and CRP evaluation.*
- *Asymptomatic patients: institute prophylaxis with Indomethacin (ER, 75 mg/day, 6 weeks) to SCI with less than 6 weeks, if risk factors for NHO are present.*
- *If suggestive symptoms arise, first exclude DVT. After, request an x-ray, for differential diagnosis and evaluate calcifications. Repeat blood tests. Proceed to bone scintigraphy for early diagnosis.*
- *Confirmed/strong suspicion NHO: initiate treatment with bisphosphonate, only in the absence of radiographic calcifications (etidronate 20 mg/kg/day, po, 6 months OR alendronate 70 mg/week, 9 months). Maintain an adapted rehabilitation program.*
- *Significant limited ROM or complications with functional impact should motivate surgery consideration. After surgery, institute recurrence prophylaxis (pamidronate).*

Conclusion: *A management protocol is proposed for prompt and accurate diagnosis and treatment of NHO in SCI patients.*

Keywords*: Ossification, Heterotopic; Spinal Cord Injuries.*

Resumo

Introdução: A ossificação heterotópica neurogénica (OHN) é uma complicação frequente da lesão medular (LM). A OHN representa um desafio diagnóstico e pode comprometer a funcionalidade do paciente. O nosso objetivo é caracterizar uma série de casos de OHN em pacientes com LM, de um centro de reabilitação, rever a

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literatura e propor um protocolo para a sua gestão.

Métodos: Descrevemos uma série de casos com base em registros médicos. Foi realizada uma revisão da literatura para etiologia, diagnóstico e tratamento de OHM em LM.

Resultados: Um total de 5 pacientes com LM foram incluídos, 3 eram do sexo masculino (idade mediana 48,9 anos). Três foram LM traumáticas, 2 tinham TCE concomitante, todos eram lesões torácicas (T4-T9), 4 eram lesões completas, 3 tinham disreflexia autonómica. O tempo mediano de LM – OHN instalação foi 2,1 meses. Todos apresentaram edema da anca. Subidas da fosfatase alcalina (FA) e da proteína C reactiva (PCR) foram documentadas.
Principais passos do protocolo:
- Avaliação do cálcio, fósforo, FA, CK e PCR
- Pacientes assintomáticos: instituir profilaxia com Indometacina (75 mg/dia, 6 semanas) em LM com menos de 6 semanas, se fatores de risco para OHN estiverem presentes.
- Se sintomas sugestivos surgirem: primeiro excluir TVP. Após, realizar raio-x para diagnóstico diferencial e para avaliar calcificações. Repetir análise sanguínea. Realizar cintigrafia óssea para diagnóstico precoce.
- OHN confirmada/forte suspeita: iniciar tratamento com bifosfonato, só na ausência de calcificações radiográficas (etidronato 20 mg/kg/dia oral, 6 meses ou alendronato 70 mg/sem, 9 meses). Manter o programa de reabilitação adaptado.
- Limitação significativa das amplitudes articulares ou complicações com impacto funcional devem motivar consideração cirúrgica. Após cirurgia, instituir profilaxia de recorrência (pamidronato em esquema)

Conclusão: É proposto um protocolo para gestão atempada e correta do diagnóstico e tratamento da OHN nos pacientes com lesão medular.

Palavras-chave: Lesão Medular; Ossificação Heterotópica.

Introduction

Neurogenic heterotopic ossification (NHO) is a pathological ectopic bone formation in the soft tissue after central nervous system damage.[1,2] NHO is a frequent complication in spinal cord injury (SCI) with a reported incidence of 10% to 53%.[2,3]

NHO pathophysiology is not completely understood. However, three conditions are cited as essential to NHO development: the presence of osteogenic precursor cells (OPC), an inducing event (e.g. damage to the blood-spinal cord barrier in the SCI), and a proper environment (e.g. a site of injury-induced hypoxia) that favors OPC differentiation.[4,5] During the early phases, the release of osteogenic and inflammatory factors prevails, creating a matrix of collagen and fibroblast with a high turnover. In the later stages, mature lamellar bone is developed.[1,2,4,6]

Several NHO risk factors have been identified: male gender, young age, smoking habits, traumatic brain injury (TBI), polytrauma, long coma duration and invasive ventilation. A correlation between higher NHO prevalence and traumatic myelopathies, complete SCI, low cervical and high thoracic lesion levels has been consistently reported. SCI complications such as pressure ulcers, spasticity and autonomic dysreflexia, have also been cited as NHO risk factors.[1-4,7]

NHO typically occurs one to four months after SCI. It is usually a periarticular formation, mostly affecting the hip (70%-90%). At installation, inflammatory signs dominate the clinical picture with sudden swelling that may be accompanied by erythema and local warmth. Localized pain may be present but only in patients with sensory sparing. The presentation can mimic other conditions such as deep vein thrombosis (DVT), neoplasm, infections or hematoma.[3]

Diagnosis remains a challenge and should combine clinical suspicion, with analytic studies and diagnostic imaging. Alkaline phosphatase (AP), creatine kinase (CK) and c-reactive protein (CRP) reflect, respectively, osteoblast activity, muscular involvement and inflammation and their analytic relative rises are suggestive of NHO.[2,3,8]

Bone scintigraphy is the gold standard for early detection of NHO, it detects NHO 2-6 weeks prior to radiographic signs.[3,9,10] Ultrasound (US) is important in the differential diagnosis (eg. DVT) and represents an early detection alternative. Even though NHO is only radiographically visible when calcifications are installed, X-ray also has a role in differential diagnosis (e.g. fractures and tumors) and in treatment planning.[3, 8-10]

NHO evolution can lead to complications such as reduced range of motion, pain, skin ulcers or nervous entrapment that can compromise patient mobility and exacerbate functional compromise and disability.[2,3] Therefore, treatment should be in place in a timely manner. Three levels of care are described in the literature: prophylactic treatment, pharmacologic therapeutic treatment, and surgical intervention.

Anti-inflammatory medication downregulates inflammatory response and prevents OPC differentiation.[4,5,10,11] NSAID are efficient in reducing NHO incidence if given early after the SCI, with relatively low efficacy when HO is already developed.[4-6,8,12] SCI patients prophylactically treated with indomethacin had a lower or delayed incidence of NHO.[5,8] However, they should be used carefully in the polytrauma patient, especially considering the possible delay in healing and fracture consolidation.[4]

Nitrogenous bisphosphonates act by increasing osteoclast apoptosis and inhibiting mineralisation.[4,10] SCI patients with scintigraphy-detected NHO treated with etidronate had a reduced incidence of radiographic NHO. This suggests that

etidronate (20 mg/kg/day, oral, for 6 months) halts NHO progression if administered early when radiographic NHO evidence is absent.[2,5,7,12,13] Alternatively, if etidronate is not available, alendronate may be used though the evidence is weaker.[12,14]

Shock waves have been proposed as a treatment for NHO, particularly before surgery. While shock waves have shown potential, namely in NHO size diminishing, ROM improvement and pain reduction, current studies are limited and the parameters used vary widely,[15-20] thus evidence is still insufficient.

Surgical resection is cited as the only effective treatment for established NHO, however, recurrence rates are high and complications relevant.[4,11,13,21] As such, resection is reserved for selected cases with important complications and significant functionality limitations.[4] Early surgical excision is now known to enhance functional outcomes, without increasing the risk of recurrence, and may reduce the risk of complications as well as enhance bone and articular cartilage health.[4,11,21] Surgical resection combined with Pamidronate treatment has proven to effectively halt secondary HO progression.[12]

Finally, the rehabilitation program itself is seldom addressed by NHO studies. In the past, articular mobilization was believed to induce muscular microtrauma and aggravate NHO formation. Currently, the beneficial therapeutic effects of soft articular mobilization and early return to the rehabilitation plan are supported with the objective of maintaining range of motion and improving physical condition.[8, 9,22]

We integrate an SCI unit from a specialized rehabilitation center where intensive and interdisciplinary inpatient rehabilitation is provided. In the last few years, we have faced the challenge of SCI patients who developed NHO after admission.

We aim to characterize a case series of NHO in SCI patients, from a rehabilitation center, review the literature and propose a management protocol.

Methods

A small case series is described based on medical records. A review of the literature for etiology, diagnosis and treatment of NHO in SCI was performed. A management protocol for NHO in SCI is proposed based in these results.

Results

Of the 5 SCI patients we diagnosed, 3 were male, 3 suffered traumatic SCI, and 2 presented concomitant TBI. Age varied between 34 and 55 years old. All were thoracic lesions (T4 to T9), and 4 were complete lesions. Three required IMV during the acute phase, 1 had spasticity and 3 had previous autonomic dysreflexia episodes.

All patients showed thigh swelling (bilateral but asymmetric in two patients), one accompanied by erythema and local warmth. None had concomitant pain. AP and CRP relative rises were seen in 4 patients. The average time from SCI to NHO installation was 2.1 months.

Case 1 had asymmetric thigh swelling from admission. After vascular surgery evaluation a DVT of the external iliac vein was assumed. An angio computed tomography (CT) revealed a voluminous expansive lesion of the soft tissues with no specific characteristics, with amorphous extensive calcifications, and the hypothesis of sarcoma or NHO were placed. In MRI the possibility of a neoformative process was not ruled out. Biopsy posed as probable diagnosis a lipomatous atypical tumor of fusiform cells. Only after extensive follow-up by Oncology specialists was NHO established as the diagnosis.

In Case 2, DVT was readily excluded. Angio CT findings, however, were described as haematoma in the muscular planes adjacent to the common femoral artery. Thus, a spontaneous hematoma was assumed. Due to the increase in thigh swelling an US was performed, displaying a doppler effect presence in the region, in favour of a vascularized structure, described as a heterogenous multiloculated collection in the context of inflammatory myositis or organized hematoma. MRI finally stated thickening and collections in the context of inflammatory myositis and NHO was established as probable diagnosis (Fig. 1). Only 2 months after, did the X-ray revealed calcifications.

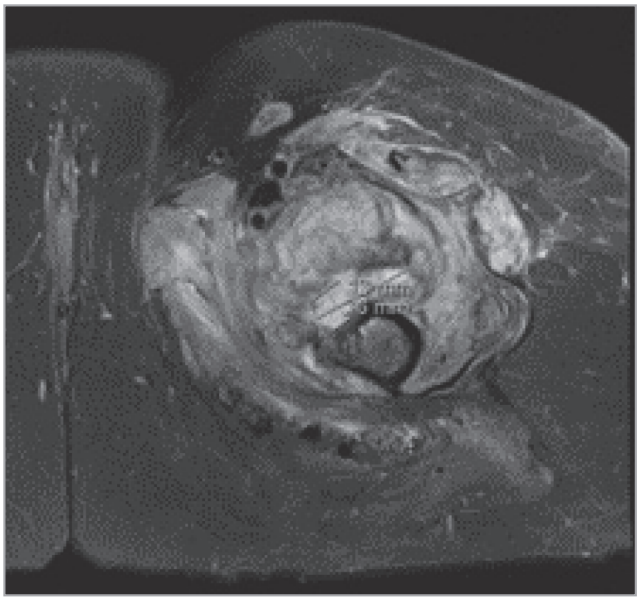

Figure 1 – MRI diagnosing NHO in Case 2.

Similarly, in Case 3 the fluid collection near the psoas iliac muscle with peripheric and muscular highlight found in angio computed tomography (CT) was first misinterpreted as a hematoma (Fig. 2A). One year later calcifications were evident bilaterally (Fig. 2B).

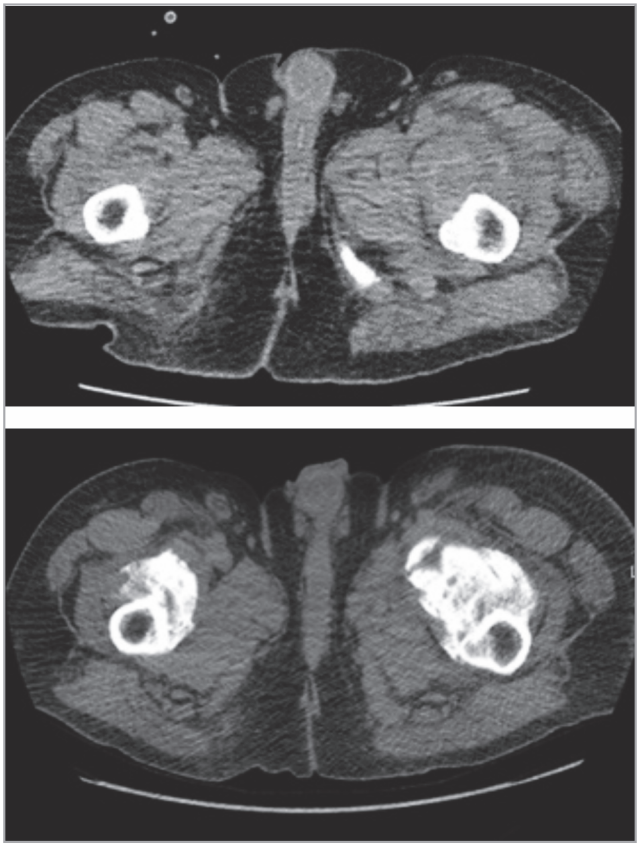

Figure 2A - Case 3 CT scan at intalation "intramuscular heamatoma"; **2B –** Case 3 CT scan 1 year later.

Case 4 underwent an X-ray at symptom installation. No fractures or calcifications were found. The ultrasonography (US) showed only increased subcutaneous echogenicity compatible with edema/ inflammation. Thigh CT suggested a possible pyomyositis, and the presence of concomitant gross calcifications pointed to NHO. After a discussion with Orthopedics a course of antibiotics and NSAID was started.

The last patient, Case 5, was previously hypocoagulated due to a pulmonary thromboembolism. The angio CT showed organized collections with edema intra and intermuscular. X-ray presented equivocal calcifications (Fig. 3). Empirical non-steroidal anti-inflammatory drug (NSAID) therapy was started. US revealed an anechoic intramuscular area with and hyperechogenic surrounding area, suggestive of partial muscle rupture. Magnetic resonance imaging (MRI) described multiples bilateral collections and hematomas. Thigh swelling persisted and the suspicion of NHO was confirmed.

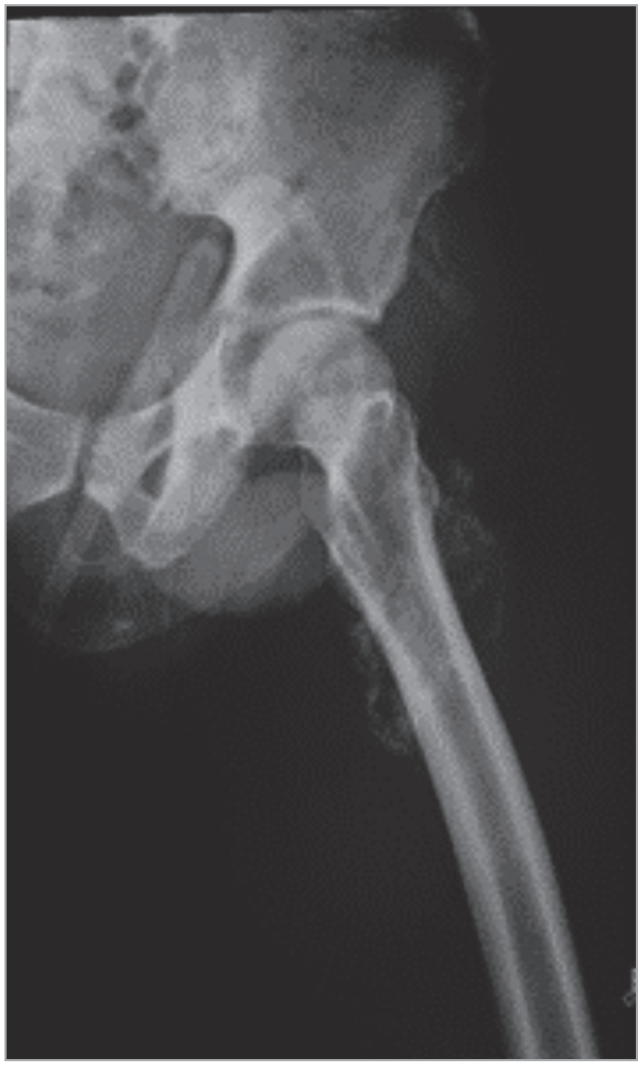

Figure 3 - Case 5 X-ray at diagnosis.

Discussion

The most frequent NHO risk factors were identified in our case series. However, contrary to literature reports most of our patients had flaccid tone. Alexander *et al* cites studies in rats injected with the toxin botulinum and presenting higher rates of NHO, suggesting that spasticity may be a consequence and not a trigger for NHO, which could explain our findings.[1] We suggest clinicians to maintain an alert state even in the absence of common risk factors.

Another highlight is the consistently challenging clinical presentation, where pain was not a signalizing symptom. Isolated thigh swelling mimics many common SCI complications, namely DVT. Proximal DVT is not as common as distal, however, given the high risk of subsequent complications, DVT's investigation is essential.[23] Nevertheless, this should be a rapid process, not blocking NHO investigation or suspicion.

Moreover, even after investigation with complementary means of diagnosis, DVT of the iliac vein, hematoma, muscular rupture, abscess, and tumor, were all named as possible diagnosis. Only two patients started treatment for NHO, both with NSAID, not following current evidence. In at least two patients the window of non-radiographic NHO for treatment was lost.

In our case series, the lack of standardized procedures delayed diagnosis and treatment, led to error and poor resource management. To implement a structured and more efficient intervention, we designed a protocol for NHO evaluation, prevention and treatment, based on the current bibliography and in our clinical practice (Fig. 4).

At admission, lower limb perimetry should be performed and blood calcium, phosphorus, AP, CK and CRP levels should be determined as base references for every patient.

As previously stated, NSAID are efficient in reducing NHO incidence if given early after the SCI. Thus, we recommend to institute prophylaxis with indomethacin LM 75 mg id per os for 6 weeks, in SCI with less than 6 weeks if risk factors for NHO are present (see above) and in the absence of contraindications. Cognitive disturbances, renal function impairment, gastric disease, coagulation disturbances and non-consolidated fractures are considered relative contraindications for NSAID prophylaxis.[4,10,11]

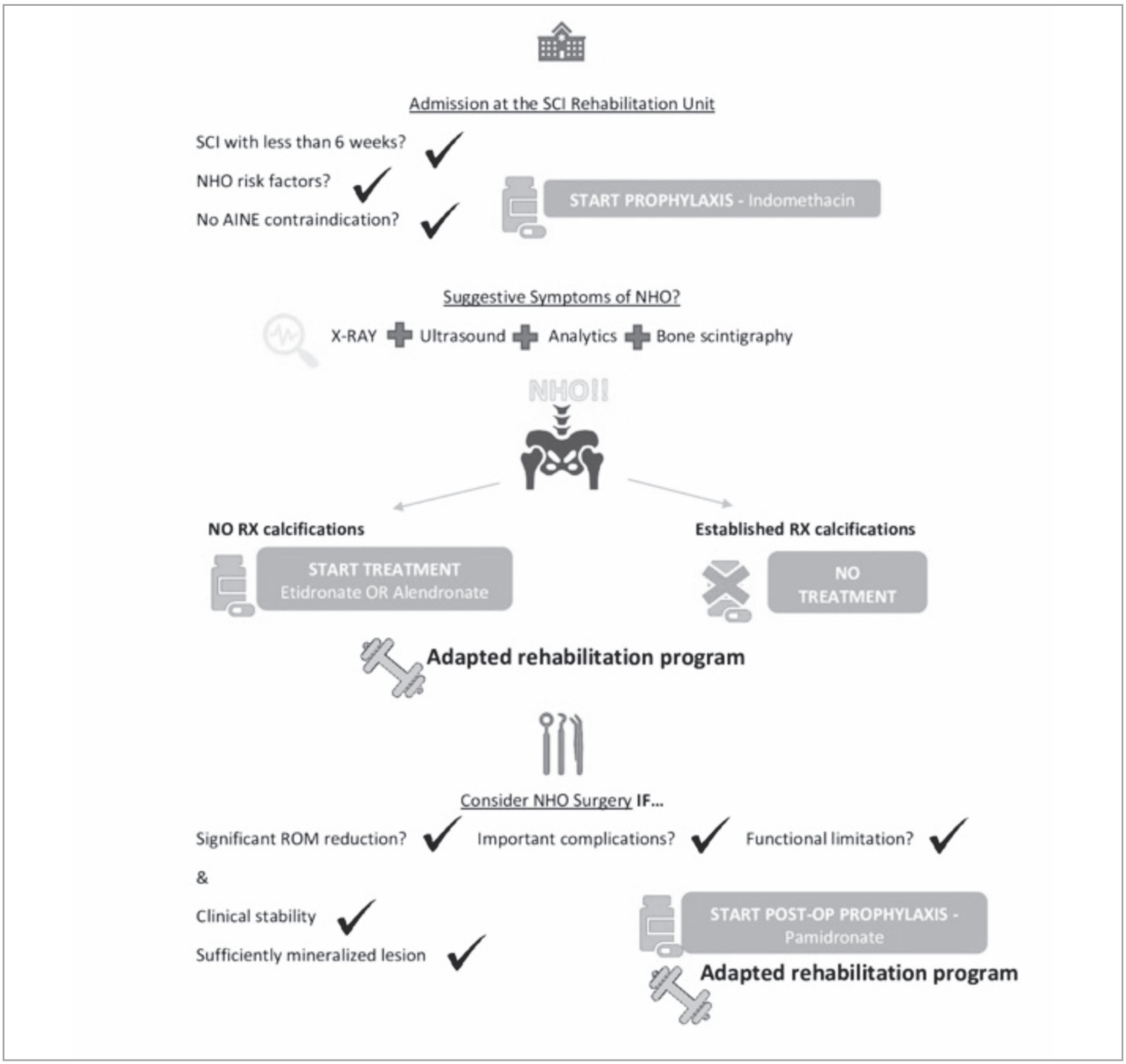

Figure 4 - Schematic version of the SCI and NHO protocol.

If the patient exhibits suggestive symptoms of NHO (e.g. sudden swelling, erythema, local warmth and/or localized pain) the first step is to exclude other pathologies. A Doppler to exclude DVT (along with D-dimer and vascular surgery evaluation, if needed) should be requested. An X-ray should be added to exclude other differential diagnoses and evaluate the presence of calcifications/stage of a possible NHO.

Analytical reassessment should be performed. AP, CK and CRP relative rises are suggestive of NHO.

Once other conditions are excluded and if the analytic study is suggestive of NHO, an US may be performed as screening (consider accessibility and operator experience). A bone scintigraphy should be undertaken for early detection and diagnostic confirmation.

With a high level of suspicion or a confirmed NHO diagnosis, treatment implementation should be considered. Pharmacological treatment should only be initiated in patients with no radiographic evidence of established calcifications, using bisphosphonate - etidronate 20 mg/kg/day, per os, for 6 months. Alternatively, if etidronate is not available, alendronate 70 mg/week for 9 months may be used. In patients with radiographic calcified NHO no pharmacological treatment is instituted.

For the acute phase of NHO formation we delineated an adapted rehabilitation program: relative rest for 1 week; soft polyarticular and multiaxial passive mobilization; cryotherapy 2-3 times/day; gradual return to the regular program as tolerated and guided by analytic improvement.

An analytic study is requested one week after the beginning of treatment to evaluate the clinical response and to rule out possible adverse effects. Follow-up is preconized after discharge in regular SCI rehabilitation appointments. Imaging studies should only be repeated if the patient shows clinical worsening or if a NHO complication is suspected.

Surgical resection is reserved for selected cases. Evaluation by an orthopedic surgeon is required if the patient fulfills the criteria for surgery proposal: significant reduction in joint range-of-motion due to NHO or associated important complications (e.g. nervous entrapment, pressure ulcer), with functional limitation. Surgery should be performed in the absence of an acute inflammatory response, when clinical stability is present and as soon as the lesion is sufficiently mineralized to allow excision.

In the immediate post-operatory period recurrence prophylaxis should be initiated with pamidronate 120 mg IV in the first 12 h, followed by progressive reduction (75>60>30>15 mg/12 h) in the next 14 days. The rehabilitation program is re-initiated, with early passive continuous/manual mobilization.

Conclusion

This review, case series and protocol intends to guide NHO care in patients with SCI. Early NHO diagnosis remains a challenge since it can mimic many common intercurrences in the SCI patient and clinical picture and imaging findings are quite unspecific. NHO installation and progression can have a negative impact on functionality and limit patients' rehabilitation program. Current treatments are not yet ideal. In the future, a better understanding of NHO pathophysiology may help define clearer screening and diagnostic criteria, uncover new treatment targets, and allow a more efficient management of NHO in SCI patients.

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