

# ORIGINAL ARTICLE

## Use of radiotherapy in immature heterotopic ossification in patients with spinal cord injury

## Uso da radioterapia na ossificação heterotópica imatura em pacientes com lesão medular

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### ABSTRACT

The incidence of heterotopic ossification (HO) in adult patients with spinal cord injuries is roughly 20%. HO usually has a benign development, but can reduce the range of joint motion and hinder the rehabilitation process. Few studies have shown the use of radiotherapy in the treatment of HO in patients with spinal cord injuries. The objective of this study is to assess whether immature heterotopic ossification progresses in patients with spinal cord injuries submitted to radiotherapy as the primary treatment. The medical records of patients attending the spinal cord injury clinic of AACD (Associação de Assistência à Criança Deficiente) with immature HO and who were treated exclusively with radiotherapy were selected. This is a historical cohort-type study. Ossification progress was determined by analysis of the range of motion of the affected joint, measurements with a goniometer and radiographic image. Ossification was classified according to the classification proposed by Brooker et al. The study follow-up period was 23.3 months. Fourteen of the 15 studied joints did not worsen clinically, nor did the HO progress. None of the patients had side effects from radiotherapy. We conclude that patients treated early with radiotherapy do not present significant HO development and that radiotherapy is a safe and easy-to-use method.

### KEYWORDS

ossification, heterotopic, spinal cord injuries, radiotherapy

### RESUMO

A incidência de ossificação heterotópica (OH) nos pacientes adultos com lesão raquimedular é de aproximadamente 20%. A OH costuma ter evolução benigna, mas pode causar redução da amplitude do movimento articular e dificultar o processo de reabilitação. Existem poucos estudos que mostram o uso da radioterapia no tratamento da OH em pacientes com lesão medular. O objetivo deste estudo é avaliar se há progressão da ossificação imatura em pacientes com lesão medular submetidos à radioterapia como tratamento primário. Foram selecionados os prontuários de pacientes da clínica de lesão medular da Associação de Assistência à Criança Deficiente (AACD) que apresentaram OH imatura e que receberam tratamento com radioterapia, sendo este o único tratamento em todos os casos. É um estudo tipo coorte histórico. Para análise da evolução da ossificação foram utilizados como parâmetros a comparação da amplitude de movimento da articulação afetada, medida com goniômetro, e a imagem radiográfica, graduando a ossificação de acordo com a classificação proposta por Brooker et al. O tempo de seguimento do estudo foi de 23,3 meses. Quatorze das 15 articulações estudadas não apresentaram piora clínica ou progressão da ossificação heterotópica. Não foram observados efeitos colaterais à radioterapia. Concluímos que os pacientes tratados precocemente com radioterapia não apresentaram progressão significativa da OH e que a radioterapia é um método seguro e de fácil aplicação.

### PALAVRAS-CHAVE

ossificação heterotópica, traumatismos da medula espinal, radioterapia

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## INTRODUCTION

The heterotopic ossification (HO) can be defined as the formation of bone in tissues that do not have the ossification property, such as muscles and the conjunctive tissue of the periarticular region, without capsule invasion.<sup>1,2</sup>

The incidence of HO in adult patients with spinal cord injury varies from 10-53%,<sup>3-6</sup> according to the diagnostic method employed and it is more frequent in the complete spinal cord injury<sup>3</sup> and is less frequent in children.<sup>5</sup>

In most cases, the HO has a benign course.<sup>2,3,6</sup> However, the HO can cause restriction in the joint range of motion (ROM) and lead to functional limitation, which hinders the rehabilitation process. The most severe cases can develop joint ankylosis.<sup>7</sup> The HO is also related to the compression of vascular and nervous structures,<sup>2,8,9</sup> and a higher incidence of pressure ulcers and deep venous thrombosis.<sup>3,10</sup>

The ossification process may be present since the first weeks up to several months after the neurological injury, with a peak incidence at around two months after the injury.<sup>6,11,12</sup>

In the acute phase, inflammatory signs are present as well as ROM decrease at the physical examination. A differential diagnosis must be carried out with deep venous thrombosis (DVT), cellulitis, osteomyelitis, tumor and fracture.<sup>2,11</sup>

The most often affected joints are the hip, elbow, shoulder and knee.<sup>2,12,14</sup> It can affect one or more joints in the same patient and in these cases, the involvement is usually bilateral.<sup>11</sup>

As the serum alkaline phosphatase (AF) is a biochemical marker of the osteoblast activity, its measurement has been used as a marker, as its increase precedes the clinical manifestations.<sup>1,2,6</sup> One must be careful when interpreting the AF levels, as its increase is also observed in the presence of fractures and liver disease.<sup>1</sup>

The plain x-ray helps the diagnosis. Usually, the radiographic signs are evident 1 to 10 weeks after the first clinical manifestations of ossification.<sup>6,7,15</sup> The first radiographic sign is the increase in the periarticular density in soft tissues, which gradually becomes a flocculated image (immature OH), followed by the maturation process where there is the formation of bone tissue (Figure 1).<sup>6</sup>



Figure 1  
Immature HO image at plain hip X-ray.

The ultrasonography can be used for an early diagnosis and follow-up; however, it depends on the examiner's experience. At the initial phase, it can be mistaken for soft tissue tumor, abscess,

hematoma or bone laceration. The Doppler ultrasound can also be useful for the differential diagnosis with DVT.<sup>16,18</sup>

The computed tomography helps the diagnosis, follow-up and guides the surgical planning. The first signs observed are the attenuation of soft tissues or muscular edema and, as the maturation occurs, the bone structure starts to become evident.<sup>2</sup>

Three-phase bone scintigraphy with technetium-99 is the method that helps the early diagnosis and the follow-up up to the maturation phase.<sup>15</sup> The HO signs in this image assessment precede the radiographic findings by four to six weeks. It is more sensitive, although less specific than the plain x-ray, as it does not differentiate HO from other inflammatory and degenerative processes, fractures, trauma or tumors.<sup>15,16</sup>

The proposed clinical treatments for HO are: non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin and COX-2 selective inhibitors;<sup>19,20</sup> biphosphonates such as etidronate;<sup>19,21-23</sup> and radiotherapy, which can be used for the treatment of the acute phase, i.e., in immature HO or associated to surgery to decrease the recidivism in the postoperative period.<sup>13, 14, 18, 24,25</sup>

The radiotherapy appeared as an effective option in the prevention of HO after hip surgeries and presented fewer adverse effects than NSAIDs and biphosphonates.<sup>15,19,22,23</sup> Few studies have shown the efficacy of radiotherapy in the treatment of HO in patients with spinal cord injury.<sup>13,14,18, 25</sup>

## OBJECTIVE

The objective of the present study was to evaluate whether there is a progression of the immature HO in patients with spinal cord injury submitted to radiotherapy as a primary treatment. This is a historical cohort study.

## METHOD

This study was approved by the Ethics Committee in Research of the Associação de Assistência a Criança Deficiente (Disabled Child Assistance Association - AACD). A total of 15,74 medical files of patients that underwent triage at the Spinal Cord Injury Clinic of AACD from February 2002 to December 2006 were analyzed. Of these, 59 (3.7%) presented signs of HO at the physical examination and had the diagnosis confirmed by plain x-ray.

We selected the medical files of patients that presented immature HO and had been referred for treatment with radiotherapy, totaling 21 cases. Eleven patients were excluded as they did not attend the routine assessments. The 10 remaining patients included in the study presented hip HO.

The radiotherapy was the only treatment in all cases and the suggested dose was 800 to 1000 cGys in a single dose on the affected joint.

Five patients were paraplegic and 5 were tetraplegic, all with complete spinal cord injury level (ASIA A). The mean age was 26.3 years (ranging from 17 to 39 years); 8 patients were males.

The comparison of the range of motion of the affected joint,

measured with a goniometer, and the radiographic image were used as parameters to analyze the evolution of the ossification, grading the ossification according to the classification proposed by Brooker et al.<sup>26</sup>

Table 1  
Classification proposed by Brooker et al.<sup>26</sup>

Grade I	Ossification foci around the hip
Grade II	Bone projection of the pelvis or proximal femur distant at least 1 cm from the opposite surface
Grade III	Bone projection of the pelvis or proximal femur decreasing the space between the opposite surface to less than 1 cm
Grade IV	Hip ankylosis

The following tests were used to analyze the results: Wilcoxon's test (Siegel)<sup>27</sup> to compare the degree of maximum hip flexion in the pre- and post-treatment periods; Kappa test (concordance) and McNemar test (discordance) to evaluate the classification of the ossification at X-ray before and after the treatment. The level for the rejection of the nullity hypothesis was set at 0.05 or 5%.

## RESULTS

All patients presented hip HO – five presented unilateral and 5 bilateral involvement, totaling 15 joints.

The time between the spinal cord injury and the HO diagnosis ranged from 3 to 7 months (mean of 4.9 months) and the time between referral and radiotherapy treatment ranged from 1 to 30 days, with a mean of 11.5 days. The mean follow-up was 23.3 months, ranging from 4 to 44 months.

Radiotherapy treatment was carried out with a single dose of 800 cGys, but in two cases, larger doses, of 2,000 and 3,200 cGys, were used. No adverse events were observed in any of the patients. At the clinical assessment, there was no worsening of the ROM in any of the cases. Nine joints maintained the ROM and six presented slight improvement (Table 2).

Before the radiotherapy, four joints presented HO classified as grade I, 3 as grade II, 7 as grade III and 1 as grade IV. After the radiotherapy, there was a progression of HO in 1 joint, which changed from grade III to grade IV; the others remained the same (Table 3).

## DISCUSSION

The HO occurs in 10-53% of patients with spinal cord injury and can become an incapacitating morbidity in the rehabilitation process of these patients.<sup>3-6</sup> The incidence of HO varies according to the diagnostic methods employed, as the scintigraphy detects the ossification at an earlier phase than the plain radiography. The earlier the diagnosis and intervention are carried out, the lower the impact on the quality of life.

At the anamnesis, it is important to consider the time of the spinal cord injury, the complaint of ROM limitation and the onset of signs and symptoms of edema, warmth, flushing and pain. The ROM is measured at the physical examination and periarticular inflammation signs can be observed. Diagnosis was confirmed

Table 2  
Maximum hip flexion measured in degrees before and after the treatment.

Joints	Pre	Post
1	90	90
2	85	90
3	100	100
4	90	100
5	40	40
6	20	20
7	70	70
8	75	75
9	80	90
10	90	90
11	70	100
12	80	90
13	80	80
14	80	90
15	90	90
X	76	81
Mi	80	90

Table 3  
Radiographic classification of HO before and after treatment.

Post	Pre			
	I	II	III	IV
I	4	0	0	0
II	0	3	0	0
III	0	0	6	0
IV	0	0	1	1
Total				15

Kappa Z Test calculated = 5.67 (p<0.001)  
McNemar Test X2= 1.00 NS  
Diagonal Concordance (unaltered) 93.3%  
Concordance above diagonal (improvement) 0.0%  
Concordance below diagonal (worsening) 6.7%

through plain anteroposterior X-ray of the pelvis and hip profile. The three-phase scintigraphy with technetium-99m is the best method for the early diagnosis of HO,<sup>15,16</sup> but it is scarcely available at the public hospitals in our country and the radiography can be used as early as during the first medical examination.

Perhaps the HO is being underdiagnosed at the asymptomatic phase and therefore, the incidence in our study was lower than the one described in the literature.<sup>3-5</sup> However, the search for new cases is carried out in all subsequent examinations, mainly during the first year of the injury. Thus, patients that were not diagnosed at the triage can still be treated.

The HO process starts around two months after the spinal cord injury.<sup>6,11,12</sup> In the present study, the mean time between the spinal cord injury and the diagnosis of HO was 4.9 months. Such difference in our series when compared to other authors can be explained by the time that it takes the patient to reach our rehabilitation center, which is, on average, 6 months. As a consequence of this time

interval, we have a higher number of mature HO cases, where the treatment is expectant, with surgical resection being indicated for the more severe cases with the objective of increasing the ROM.

The most often affected joint was the hip, in accordance with the observation made by other authors.<sup>2,6,11-14,24</sup> We had one case of elbow and two cases of knee HO; however, all of them were structured cases and thus, radiotherapy was not indicated. As all the studied cases had the HO located in the hip, we used the classification criterion proposed by Brooker et al,<sup>26</sup> which was designed to grade the severity of the radiographic aspect of the HO after total hip arthroplasty. The HO considered to be immature was the one that presented cotton-like image at the plain X-ray; when the HO is structured, the image becomes similar to bone, with the same density and well-defined borders.

The choice of radiotherapy as primary treatment is due to the fact that it is easy to apply in a single dose as well as the absence of adverse events described so far at the recommended dose.<sup>13,14,18,24,25</sup>

In the past, we used other choices of treatment, such as indomethacin and etidronate. However, these drugs were administered for long periods, from weeks to months, and several adverse events were observed, mainly gastrointestinal ones, in addition to being a high-cost treatment for the patient. There was a high incidence of treatment withdrawal and, with the interruption of the treatment with etidronate, we observed a progression in the ossification in some cases – such observation has been described by other authors.<sup>6</sup> The radiotherapy emerged as an effective modality of treatment for the HO prevention in orthopedic hip replacement surgeries.<sup>24</sup> There are few studies<sup>13,14,18,25</sup> reporting on the use of radiotherapy for the primary treatment of HO in patients with spinal cord injuries. The dose used is 800 to 1.000 cGy and it is a low dose with anti-inflammatory effect. The time of follow-up of our study 23.3 months (varying from 4 to 44 months). During this period, no clinical worsening was presented by any of the patients and no adverse events were observed with the proposed treatment.

Fourteen of the 15 joints did not present worsening or new ossification foci; one joint presented progression of the ossification, going from grade III to grade IV, according to the classification by Brooker et al,<sup>26</sup> but the ROM remained unaltered. In the most severe case, where the patient presented a high decrease in ROM and grade IV HO, the radiotherapy was used with the objective of stabilizing the ossification for subsequent surgical resection.

None of the patients presented worsening of the ROM and 9 joints presented slight ROM improvement. Since the beginning of the follow-up the patients were advised to maintain passive kinesiotherapy without abrupt movements to prevent microtrauma in an attempt to preserve the ROM. We believe that the ROM improvement is also due to the rehabilitation process and not only to the use of radiotherapy. There was no improvement in the radiographic image in any of the cases. The two studies carried out by Sautter-Bihl et al<sup>13,14</sup> did not demonstrate regression, either.

## CONCLUSION

We conclude that the patients submitted to an early treatment

with radiotherapy did not present a significant HO progression and that radiotherapy is a safe and easy-to-apply treatment method. Randomized prospective studies, comparing the efficacy and the cost-benefit of the radiotherapy and other forms of treatment for post-spinal cord injury HO are necessary.

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