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Incidence and risk factors in the appearance of heterotopic ossification in spinal cord injury

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Heterotopic ossification (HO) is a frequent complication in patients with a spinal cord injury (SCI), although the aetiology is unknown. A study was undertaken of 654 SCI patients with traumatic aetiology, admitted for the first time to the Hospital Nacional de Paraplejicos, Toledo, during 1988 and 1989. Of the total number of patients, 85 (13%) were diagnosed HO and 569 without HO. The diagnosis was mainly achieved by x-ray studies and clinical signs. From the 569 patients with traumatic aetiology without HO, 44 were selected at random, as were 44 of the 85 patients with HO. The mean time lapse between the occurrence of the accident and admission for patients with HO was 40.79 days (typical deviation (TD) = 45.2), and for patients without HO was 32.84 (TD = 38) days, resulting in a value of F = 0.796 through analysis of variance, which is not a statistically significant variation between the 2 groups. In both groups we have taken account of the following variables: age at time of lesion, lesion level, type of lesion (complete or incomplete), spasticity, urinary tract complications, deep vein thrombosis, important associated injuries occurring at the moment of lesion, time elapsed before admission and the existence of pressure sores. In those SCI patients with HO the number of ossifications and their localisations were also verified.

By use of the chi square test (X^2) over all 9 variables which were studied, we found that 3 variables (complete spinal lesion, presence of pressure sores and spasticity) were significantly related to HO formation. The risk factors appear to be cumulative: the presence of 2 risk factors in the same patient was found to result in HO appearing in 65 ± 8% (P ± SP), and when all the risk factors are present in the same patient, 85 ± 7.9% had heterotopic ossification.

Eighty two per cent of the patients who presented pressure sores had a time lapse to admission of more than 15 days, against 18% of those whose time lapse to admission was less than 15 days $X^2[1] = 17.8$, $p < 0.001$. For those patients whose time to admission was less than 15 days, and whose progress we could follow from the start, from a total of 7 patients with sores, 6 developed HO while one did not, $X^2[1] = 4.2$, $p < 0.05$.

Keywords: spinal cord injury; heterotopic ossification; risk factors.

Introduction

Heterotopic ossification (HO) consists in the appearance of new bone within the soft tissues surrounding peripheral joints.[1,2] Its aetiology is unknown, although various hypotheses exist, including mesenchymal metaplasia,[3–5] bone metabolism,[6,7] biochemical factors[8] and joint trauma.[9–11] It is a complication frequently found in patients with spinal cord injury, and although it can appear in any joint, tends to appear in the hip joints and to a lesser degree, in the shoulders, knees and elbows.[12–14] It is of variable extent; and between 3%–8% of patients who develop HO go on to total ankylosis.[15,16] Parameters indicative of stabilisation and maturity of HO which have been used include, among others: alkaline phosphatases[17,18] alkaline phosphatases in combination with high levels of phosphorous,[19] hydroxyproline,[20] collagen metabolites[21] and series study stability in capture of Sr 87.[22]

Pharmacological treatment using disodium etidronate has been tried, with the aim of reducing incidence of recurrence of HO following surgery.[23–25] Early rehabilitative treatment lowers the incidence, whilst forced sudden movement can increase it,[1,9] but very little acceptable documentation exists, and there is a lack of real criteria for the prediction of which spinal injury patient will be most likely to develop HO.

Considering these premises, we have tried to interrelate a series of parameters which commonly occur in spinal injury patients accompanied by HO, in an attempt to discover if the risk prediction for HO is possible within the population of SCI patients. If this was the case, then early diagnosis and prophylactic treatment of those patients most at risk could reduce the incidence, severity and the likelihood of complications with HO.

Materials and methods

A total of 654 SCI patients with traumatic aetiology admitted for the first time to the Hospital Nacional de Paraplejicos in Toledo were examined during 1988 and 1989. Of this total, 85 (13%) were identified as having HO and 569 no HO. Diagnostic criteria for HO were clinical signs and the appearances on x-ray examinations.

From these 85 patients with HO, 44 were randomly selected (using random numbers). A sample of 44 other patients without HO was also selected, using the same technique. All those patients whose time lapse to admission was greater than 180 days were excluded from both groups. Mean time elapsed from accident to hospital admission for patients with HO was 40.79 days and 32.84 days for those without HO, giving a value of $F = 0.796$ using analysis of variance, which does not show a statistically significant variation between the 2 samples (Table I). The following characteristics were studied in all patients of both groups: age at the moment of SCI occurrence; time elapsed from lesion to admission to our hospital; lesion level (cervical, thoracic and lumbar); type of lesion (complete or incomplete); spasticity; complications of the urinary tract; deep vein thrombosis; other trauma occurring at the time of the accident; and pressure sores. For spasticity, we have taken account of patients' treatment using antispasticity drugs, although cases have not been classified according to severity. Two patients with horse tail type lesions were found among those with HO, and 3 in the sample without HO. For complications of the urinary tract, we have taken account of lithiasis, diverticulum, reflux, ectasia, pyelonephritis, and surgical interventions at sphincter level. All pressure sores have been included, although neither their degree nor severity has been taken into account. The number and sites of heterotopic ossification were also studied in the HO sample.

The statistical study has taken the following factors into account; the arithmetical mean (M), typical deviation (TD) standard error of the mean (SM), and standard deviation in mean differentiation (SD). Percentages (P) have been used for the qualitative variables, with standard percentage error (SP) and the chi square test (X^2).

Results

No statistically significant differences were found between the ages of patients with and without HO. The average age of HO patients was 29.7 ± 1.4 ($M \pm SM$) years (over a range of from 18 to 56 years old), and that of patients without HO was 33.3 ± 1.9 years (from 17 to 64 years old), with a differentiation of the mean ages $\pm$ the standard error in mean differentiation of 3.6 ± 2.3, which is not significant.

Twenty four patients were found to have only one HO, 17 with 2, one with 3 and 2

Table I Mean time lapse lesion/admission in days for HO and non HO patients.

	Mean	Typical deviation	Size	Significance
With HO	40.79	45.2	44	F = 0.796 NS
Without HO	32.84	38	44	

with 4. Hips were the most frequent site of HO, in 36 (82%) patients, and of these 18 (41%) had both hips involved: 10 (23%) only in the left hip and 8 (18%) only in the right hip. Other locations were: 4 in knees (9%), 3 in shoulders (7%) and one (2%) in elbow joints.

Table II shows the factors studied in which no statistically significant differences have been found between patients with and without HO. These are: deep vein thrombosis, complications of the urinary tract, level of lesion and important associated traumas which occurred at the moment of the injury.

Statistical analysis using the chi square test has shown that higher significant statistical differentiation in the following factors exist in patients with HO: complete spinal lesions 40 (91%), compared with incomplete lesions 4 (9%), together with a higher percentage of complete lesions in HO patients, 40 (56%) higher than in those without HO 31, (44%), $X^2[1] = 4.66$, $p < 0.05$) (Table III).

Pressure sores and HO are clearly interrelated, as can be appreciated from Table III. More patients, 27 (61%) with HO present pressure sores than do not, 17 (39%), and more patients with HO, 27 (69%) present pressure sores than do patients without HO, 12 (31%), $X^2[1] = 9$, $p < 0.01$.

Spinal cord injury with spasticity is more prevalent among patients with HO (30 (68%)) against 14 (32%) without spasticity. Table III also shows that more patients with HO present spasticity, 30 (67%), against those without HO, 15 (33%), $X^2[1] = 8.9$, $p < 0.01$.

The following significant risk factor variables have been found in relation to the appearance of HO: complete spinal lesion, pressure sores and spasticity. The relationship of these factors according to their presentation in patients with and without HO was studied. The number of risk factor variables on a scale of 0–3 for the sum of the 2 samples has therefore been shown. This

Table II Non significant variables

Variables	With HO N = 44	Without HO N = 44	Significance
Lesion level			
Cervical	21 (48%)	17 (39%)	$X^2[2] = 1$ NS
Thoracic	20 (45%)	22 (50%)	
Lumbar	3 (7%)	5 (11%)	
Vein thrombosis	14 (32%)	10 (23%)	$X_2[1] = 0.52$, NS
Urinary tract complications	14 (32%)	8 (18%)	$X^2[1] = 1.5$, NS
Associated trauma	24 (55%)	21 (48%)	$X^2[1] = 0.18$ NS

Table III Risk factors and heterotopic ossification

Risk factors	With HO	Without HO	Significance
Type of lesion			
Complete	40	31	$X^2[1] = 4.66$, $p < 0.05$
Incomplete	4	13	
Pressure sores			
With sores	27	12	$X^2[1] = 9$, $p < 0.01$
Without sores	17	32	
Spasticity			
With spasticity	30	15	$X^2[1] = 8.9$, $p < 0.01$
Without spasticity	14	29	

runs from 0 for patients who do not have any risk factors, to 3 for those with all 3 factors (Table IV), with a significant statistical differentiation of $X^2[3] = 26.8$, $p < 0.001$. As can be observed from this table, risk factors are cumulative. With 2 risk factors there is a 65 ± 8% (P ± SP) probability of HO occuring, and with 3 factors 85 ± 7.9% probability of HO.

Table V shows that the time elapsed before an SCI patient is admitted to a specialised unit is related to the appearance of pressure sores. Of the 39 patients who presented with pressure sores, 32 (82%) had taken more than 15 days following the accident before being admitted to our hospital, against 7 (18%) who took less than 15 days, $X^2[1] = 17.8$, $p < 0.001$.

As can be observed in Table VI, for patients whose time lapse to admission was less than 15 days, and whose development could be followed from the first, of the 17 with HO, 6 (35%) presented pressure sores, compared with one patient (4.5%) who developed pressure sores of the (n = 22) patients without HO, $X^2[1] = 4.2$, $p < 0.05$, giving a correlation pressure sores/HO.

Patients with complete lesions and HO (n = 40) were more likely to have pressure sores 24 (60%) than were patients with complete lesions without HO (n = 31), 9 (29%), $X^2[1] = 5.5$, $p < 0.05$.

Table IV Relationship of risk factors and heterotopic ossification in SCI

Risk factors 0–3	With HO n = 44	Without HO n = 44	Patients n = 88
With 0	1(25%)	3(75%)	4
With 1	6(18%)	27(82%)	33
With 2	20(65%)	11(35%)	31
With 3	17(85%)	3(15%)	20

$X^2[3] = 26.8$, $p < 0.001$

Discussion

According to the different series, the incidence of HO varies between 12% and 40% of patients.[9,13–15,26,27] Our incidence of 13% is similar to that given by other authors in recent years.[28,29] The period of the highest frequency of occurrence is from one to 4 months following the spinal lesion, although it can occur even after a year.[23,25]

The presentation of HO has been correlated with infections of the urinary tract, pressure sores, spasticity, vigorous manipulation, alterations in the innervation of the sympathetic nervous system, changes in collagen and in bone metabolism, metabolic acidosis and disturbances in ionic balance, vascular alterations, and the time that has elapsed before admission to a specialised unit, etc.[19,13,21,22,28–30] We believe that localised multifactorial mechanisms must exist,

Table V Relation of time lapse from lesion to admission, to number of patients with pressure sores

Time to admission	With sores	Without sores	Significance
Less than 15 days	7	32	$X^2[[1] = 17.8$, $p < 0.001$
More than 15 days	32	17	
Total	39	49	

Table VI Relation of time to admission less than 15 days and number of pressure sores in patients with and without HO

	With HO	Without HO	Significance
With sores	6	1	$X^2[1] = 4.2$, $p < 0.05$
Without sores	11	21	
Total	17	22	

together with other general factors resulting from the neurological lesion and its metabolic and vegetative repercussions. Our study has found 3 risk factors: complete transverse spinal lesion, pressure sores and spasticity. Most authors find a higher incidence of HO in patients with complete transverse spinal lesions, than in those whose lesions are incomplete.[14,27,29] Although pressure sores can appear before or after the onset of HO, they usually do so beforehand, and are generally caused by lack of special care during the acute phase, if this is spent in a non specialised hospital. Several authors have emphasised the importance of rapid admission to a specialised hospital, as they believe that this diminishes the number of patients who subsequently develop HO.[1,9] Our study has found time lapse to admission to a specialised hospital to be related to pressure sores: an increase in delay giving rise to an increase in the number of pressure sores. Another finding was that if these sores appear during the early phases of the condition, then this influences the onset of HO. We understand this to mean that the same aetiology could play a role in both the development of sores and the formation of HO, ie pressure, severe friction or muscular trauma, together with lack of special care, with tissue infection perhaps playing a role following development of a pressure ulcer. Heterotopic ossification could be due to the presence of pressure sores, if the infection penetrates the deep tissues down to bone.[31]

Lal *et al*[29] found that 84% of their patients with HO present had spasticity, against 54% of those without HO. Our study has also found statistically significant differences, showing greater predominance of spasticity in HO than in non HO patients. Whilst the onset of spasticity usually occurs during the first few weeks after the spinal lesion, HO develops after several weeks or months.[29]

Trauma to the joints and violent manipulation, above all of those patients suffering intense spasticity, have been stated to be risk factors for the appearance of HO by several investigators.[9,22] We believe that trauma, manipulations and even intense spasticity in patients lacking sensitivity can give rise to the formation of haematomas and para-articular microhaematomas, which then calcify and ossify through metaplasia of the mesenchymal cells into osteoblasts.

The risk factors encountered appear to be cumulative. The presence of 2 factors gives rise to the probability of $65 \pm 8\%$ of developing HO, this rising to $85 \pm 7.9\%$ for 3 factors. For these cases, the possibility of prophylactic treatment using disodium etidronate should be considered.

Correct rehabilitative medical treatment from the moment of occurrence of the lesion diminishes some risk factors intervening in the aetiology of HO.

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