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ORIGINAL ARTICLE

Ankylosing spondylitis does not increase the risk of neurogenic heterotopic ossification in patients with a spinal cord injury: a retrospective cohort study

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Study Design: Retrospective chart review.
Objectives: The present study was performed to analyze the impact of ankylosing spondylitis (AS) in developing heterotopic ossification (HO) in patients following spinal cord injury.
Setting: Department of Spinal Cord Injury and Department of General and Trauma Surgery, BG-University Hospital Bergmannsheil Bochum, Ruhr-University Bochum, Germany.
Materials and Methods: Between January 2003 and December 2015, 67 patients with AS and SCI were included in the study. The control group consisted of 141 patients with SCI and without AS. The definitive diagnosis of HO was made via magnetic resonance imaging or computed tomography. Primary outcome measure was to analyze the impact of AS on the development of HO.
Results: Fifteen out of 67 AS patients (22.4%) had a diagnosed HO. In the control group, 28 of 141 patients (19.9%) suffered from HO. Patients with AS had no significant higher risk for HO development compared with patients without AS (RR = 1.16; 95% CI = 0.65–2.09). However, patients with a complete neurological deficit had a twofold higher risk for HO development (RR = 2.55; 95% CI = 1.26–5.16).
Conclusions: AS does not increase the risk for HO development in patients with spinal cord injury.
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INTRODUCTION

Heterotopic ossification (HO) is the presence of bone in non-skeletal tissue and can occur in up to 22% of patients with spinal cord injury (SCI).[1,2] It may cause severe limitation of the range of motion of the patient's joints, increasing the burden of the disease. Despite its high incidence, the exact pathogenesis of HO is still unknown. Previous research has identified several risk factors for the development of HO. These are as follows: local micro-trauma, unbalance of calcitonin and parathyroid hormone levels, genetic predisposition, immobilization or venous stasis.[1,2] Known clinical risk factors are as follows: concomitant thoracic trauma; a complete lesion (AIS A); the presence of spasticity or pneumonia; and having required a tracheostomy.[1,3]

Ankylosing spondylitis (AS) is a seronegative spondyloarthropathy associated with the presence of the HLA-B27 gene that causes erosions and ankylosis of the spine and of the sacroiliac joints. The presence of AS has been identified as a risk factor for HO development in patients who undergo total hip arthroplasty (THA). In a recent review, Zhang *et al.*[4] reported a twofold elevation of the risk of developing HO in patients with AS following THA.

The impact of AS on HO in spinal cord-injured patients remains unknown. A literature search revealed no recent studies addressing this question, only decades-old studies with different claims on the influence of AS and HLA-B27 on spinal cord-injured patients. In 1981, Larson *et al.*[5] reported on the increased prevalence of HLA-B27 in patients with ectopic ossification following traumatic SCI. In contrast to this study, Garland *et al.*[6] concluded in 1984 that there was no positive correlation between the HLA antigen system and HO onset subsequent to brain trauma or SCI. However, to our knowledge, there is no reliable evidence indicating whether AS increases the risk of developing HO in spinal cord-injured patients.

The main objective of the current study was to determine whether AS increases the risk for the development of HO in spinal cord-injured patients. A secondary aim was to describe the demographic characteristics, clinical variables, injury patterns and complications of this group of patients.

MATERIALS AND METHODS

This retrospective cohort study was conducted after obtaining approval from our institutional review board. Patients over the age of 18 years with a traumatic SCI and a concomitant diagnosis of AS, and those who were treated in the Department of Spinal Cord Injuries at our University Hospital between January 2003 and December 2015 were eligible for the study. Those patients with a confirmed diagnosis of AS were enrolled as the exposed group ($N = 67$). A twice-large group of spinal cord-injured patients without AS was randomly selected and enrolled into the unexposed group ($N = 141$).

The main outcome variable was a confirmed diagnosis of HO. The diagnosis of HO was accomplished using a previously described protocol. According to

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this protocol, patients are screened biweekly by ultrasound examinations of the hip and shoulder joints by our experienced radiologists. In case of suspicion for HO, the presumptive clinical diagnosis was confirmed with either computed tomography or magnetic resonance imaging.

Information about the following variables was collected from the medical records for all patients: date of birth, sex, severity of spinal cord lesion according to the American Spinal Injury Association (ASIA) impairment scale (AIS),[7] mechanism of injury, time interval between the SCI and HO diagnosis (in days), length of hospital stay, laterality of the HO lesion, spasticity, thoracic injury, pressure ulcers, pneumonia and tracheostomy.

Statistical analysis

The relative risk of developing HO in spinal cord-injured patients with AS was estimated using a generalized linear model with a Poisson distribution, a log link and a robust variance estimator.[8,9] To adjust for confounding, the following predictors were selected a priori based on previous research and were also included in the model: spasticity, thoracic injury, complete SCI, pressure ulcers, pneumonia and tracheostomy.[1] Confidence intervals at the 95% level were calculated over 200 bootstrap repetitions.[10,11] Descriptive statistics are presented for all other variables. All analyzes were performed using Stata/MP 13.0 for Windows (StataCorp LP, College Station, TX, USA).

RESULTS

Complete data for all variables of interest were collected for all patients in the study. No patient was excluded because of missing data. In total, 208 patients were included in this study: 67 patients were enrolled into the AS group and 141 patients were enrolled into the No AS group. As shown in Table 1, both groups had a similar distribution of demographic and clinical variables.

The exposed patient cohort consisted of 57 male (85.1%) and 10 female patients (14.9%), with a mean age of 68.1 years (37–88 years; s.d. = 11.6). Thirty-three patients were paraplegic (49.3%) and 34 patients were tetraplegic (50.7%). Thirty-three out of 67 patients (49.3%) had a complete lesion according to the ASIA impairment scale (AIS A); five patients (7.5%) had an AIS B lesion; nine patients (13.4%) had an AIS C lesion; and twenty patients (29.9%) had an AIS D lesion.

All patients had a traumatic SCI. The most common reason was a simple fall, for example, from a step (48 patients, 71.6%), followed by vehicle accident (9 patients, 13.4%). Forty-three patients underwent surgery within 72 h of admission (64.2%), twenty-one patients were treated after 72 h (31.3%) and three were treated conservatively. The predominant surgical technique was a dorsal spondylodesis (39 patients, 58.2%), followed by 15 patients who received a dorso-ventral spondylodesis (22.4%).

Out of 67 patients with AS, 15 (22.4%) had a confirmed diagnosis of HO, compared with 25 out of the 141 (17.7%) patients without AS.

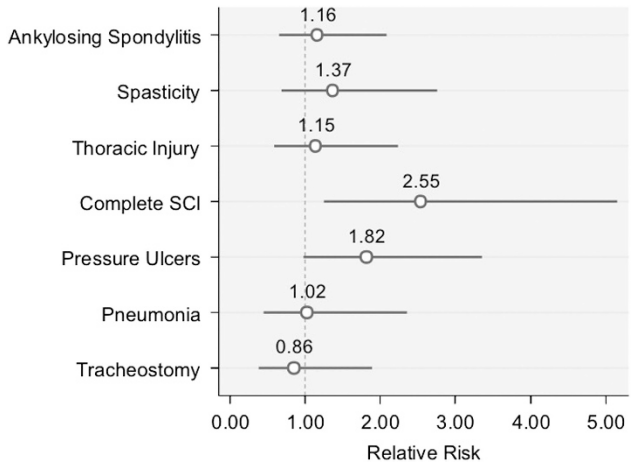

Figure 1 The relative risk values; AS is not a significant risk factor.

Table 1 Clinical characteristics of the two groups of spinal cord-injured patients with and without AS

	No AS		*AS*		*Total*	
	No.	*%*	*No.*	*%*	*No.*	*%*
No HO	116	82%	52	78%	168	81%
Hip HO	25	18%	15	22%	40	19%
Right hip HO	4	17%	0	0%	4	11%
Left hip HO	4	17%	2	17%	6	17%
Bilateral HO	16	67%	10	83%	26	72%
Female sex	28	20%	10	15%	38	18%
Male sex	113	80%	57	85%	170	82%
AIS A	62	44%	33	49%	95	46%
AIS B	5	4%	5	7%	10	5%
AIS C	17	12%	9	13%	26	13%
AIS D	57	40%	20	30%	77	37%
No spasticity	104	74%	50	75%	154	74%
Spasticity	37	26%	17	25%	54	26%
No thoracic injury	84	60%	36	54%	120	58%
Thoracic injury	57	40%	31	46%	88	42%
Incomplete SCI	79	56%	32	48%	111	53%
Complete SCI	62	44%	35	52%	97	47%
No pressure ulcers	107	76%	46	69%	153	74%
Pressure ulcers	34	24%	21	31%	55	26%
No pneumonia	76	54%	26	39%	102	49%
Pneumonia	65	46%	41	61%	106	51%
No tracheostomy	68	48%	32	48%	100	48%
Tracheostomy	73	52%	35	52%	108	52%

Table 2 Distribution of clinical characteristics in spinal cord-injured patients by occurrence of HO

	No HO		*Hip HO*		*Total*	
	No.	*%*	*No.*	*%*	*No.*	*%*
No AS	116	69%	25	63%	141	68%
AS	52	31%	15	38%	67	32%
Female sex	34	20%	4	10%	38	18%
Male sex	134	80%	36	90%	170	82%
AIS A	66	39%	29	73%	95	46%
AIS B	8	5%	2	5%	10	5%
AIS C	21	13%	5	13%	26	13%
AIS D	73	43%	4	10%	77	37%
No spasticity	126	75%	28	70%	154	74%
Spasticity	42	25%	12	30%	54	26%
No thoracic injury	99	59%	21	53%	120	58%
Thoracic injury	69	41%	19	48%	88	42%
Incomplete SCI	99	59%	12	30%	111	53%
Complete SCI	69	41%	28	70%	97	47%
No pressure ulcers	130	77%	23	57%	153	74%
Pressure ulcers	38	23%	17	43%	55	26%
No pneumonia	85	51%	17	43%	102	49%
Pneumonia	83	49%	23	57%	106	51%
No tracheostomy	83	49%	17	43%	100	48%
Tracheostomy	85	51%	23	57%	108	52%

The mean time interval between the initial trauma and the diagnosis of HO was 59.9 days ± 31.2 (range, 19–143 days). In the majority of the cases, HO affected both hips (13 patients, 86.7%). In the remaining two cases (13.3%), HO occurred unilaterally. Bursitis trochanteric occurred in 4 of 15 HO patients (26.7%). Five of fifteen HO patients received NSAID in the form of Ibuprofen. All patients received a therapeutic radiation, with 13 patients (86.7%) receiving 7 Gy and 15 MeV and the remaining two patients (13.3%) were treated with 7 Gy and 6 MeV. In two cases, HO recurrence (13.3%) occurred. In these cases, after a repeated radiation therapy with 7 Gy and 15 MeV, no HO relapse occurred. No patient developed any side effects related to the radiation therapy. In the control group, 28 out of 141 patients (19.9%) suffered from HO.

The risk of HO was not significantly higher for patients with AS (RR = 1.16; 95% CI = 0.65–2.09) (Figure 1). However, patients with a complete neurological deficit had more than a twofold increase in the risk of HO development (RR = 2.55; 95% CI = 1.26–5.16) (Figure 1). The risk of HO increased almost twofold (RR = 1.82; 95% CI = 0.99–3.35) in the presence of pressure ulcers. Table 2 shows the clinical characteristics of the patients distributed by outcome.

During the hospital stay, 7 patients suffered from deep vein thrombosis, 2 patients had a pulmonary embolism, 41 patients suffered from pneumonia and received antibiotic treatment, and 21 patients developed a pressure sore. The most common localization for pressure ulcers was the sacral region (15 patients, 71.4%), which mainly impressed with second-grade severity according to the European Pressure Ulcer Advisory Panel Classification (13 patients, 61.9%).[12]

DISCUSSION

To our knowledge, this is the largest retrospective study on the relationship between AS and the development of HO following a SCI. We found no evidence that AS increases the risk of HO in spinal cord-injured patients. Only the completeness of the lesion and the presence of pressure ulcers showed an increase in the risk of developing HO in this cohort.

The relationship between AS and the development of HO has been previously described for patients who undergo THA.[13] Zhu *et al.*[14] conducted a meta-analysis of the risk factors of HO in THA patients, reporting an elevated occurrence of HO in patients with AS.

In contrast, our study results present that AS does not increase the risk for HO development in patients with SCI.

The prevalence of HO in AS patients seems to be decreasing over time,[15] with the HO prevalence in AS patients following THA reported in 1967 as 62%, whereas in 2012, the prevalence was reported as 6.4%. As discussed by the authors, evolving surgical techniques, such as minimally invasive procedures, or innovations in implant design, may have helped lower the incidence of HO after THA.

In comparison to the current reports on the prevalence of HO in THA, the prevalence of around 20% observed in spinal cord-injured patients in this study seems relatively high. In the special case of neurogenic HO in SCI patients, this prevalence fits into the observations of average HO occurrence in patients without AS: In 2012, Citak *et al.*[1] reported on a HO incidence in SCI patients of 21.9%. A similar incidence of HO with 20% has already been reported in 1992 by Wittenberg *et al.*[2] Interestingly, the incidence of HO did not change over the last 20 years, although the surgical technique (for example, percutaneous stabilization) has changed over the years.

One reason for the continuing high prevalence of HO in SCI patients might be the different pathogenesis of neurogenic and traumatic HO development, especially the fact that patients with a complete neurological deficit had a significantly higher risk of HO development. Another explanation might be the fact that patients with a concomitant pelvic trauma have no significant increase in HO incidence. We assume that the pathogenesis of neurogenic HO is not associated with local trauma of the affected area. In the largest clinical study analyzing the clinical risk factors for HO, Citak *et al.* reported on the relationship between HO development and several factors, such as pneumonia, thoracic trauma, and the presence of a tracheostomy. All those factors are associated with inflammatory reactions of the lung. Those parameters might be a key factor for HO development, as it is also known that lung disease may lead to new bone formation. Various possible mechanisms for this effect have been proposed, including nerve stimulation, secretion of growth factors and overproduction of prostaglandin E2.[16–19]

In conclusion, our study showed that patients with AS are not at higher risk for HO development, whereas patients with a complete neurological deficit have a two-fold higher risk of developing HO. Adequate regular screening of patients with a complete neurological deficit could increase the number of early detected HO.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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