J Musculoskelet Neuronal Interact 2014; 14(1):19-28

Original Article

Hylonome

Prevalence and risk-factors of neurogenic heterotopic ossification in traumatic spinal cord and traumatic brain injured patients admitted to specialised units in Australia

J.E. Reznik[1], E. Biros[2], R. Marshall[3], M. Jelbart[4], S. Milanese[1,5], S. Gordon[1], M.P. Galea[1,6]

[1]Physiotherapy, James Cook University, Townsville, QLD 4811, Australia; [2]Queensland Research Centre for Peripheral Vascular Disease, Townsville, QLD 4811; [3]Amputee & Spinal Injury Rehabilitation Service, Hampstead Rehabilitation Centre/Royal Adelaide Hospital, Adelaide, S.A., Australia; [4]Brain Injury Rehabilitation Service, Hampstead Rehabilitation Centre, Adelaide, S.A., Australia; [5]Physiotherapy, University of South Australia, Adelaide, S.A., Australia; [6]Department of Medicine, (Royal Melbourne Hospital) The University of Melbourne, VIC 3010, Australia

Abstract

Objectives: To identify the prevalence and risk factors in the development of Neurogenic Heterotopic Ossification (NHO) in traumatic brain and spinal cord injured patients admitted to specialised units. **Methods:** An audit protocol was used to gather all clinically relevant data, in specific patient groups, relating to the prevalence of NHO, and was statistically analysed to identify traumatic brain injury (TBI) and traumatic spinal cord injury (TSCI) patients at high risk of developing NHO. **Results:** 262 TBI and 151 TSCI patients were identified. NHO was diagnosed in 10 and 16 patients with TBI and TSCI, respectively; 18 clinically relevant characteristics were analysed for association with NHO in these patient groups. The only common variables associated with NHO in both neurological conditions were deep vein thrombosis and/or pulmonary emboli (DVT/PE). **Conclusions:** The prevalence of NHO in TBI patients is less than one-third of that found in TSCI patients, ~4% and 11%, respectively. This study also suggests that the risk factors associated with NHO in TBI patients are distinct from those identified as risk factors in TSCI patients.

Keywords: Brain Injury, Spinal Cord Injury, Traumatic, Neurogenic Heterotopic Ossification

Introduction

Heterotopic Ossification (HO) is defined as the formation of lamellar bone-like structures inside soft-tissues where bones do not normally exist[1-3]. The condition was first noted in children with fibrodysplasia ossificans progressiva (FOP) by Patin in the 17th century[4] and later described in more detail in World War I veterans, paraplegic from intramedullary gunshot wounds[5]. HO is usually acquired following trauma such as major surgery, e.g. hip arthroplasty, burns, fractures, dislocations, and soft-tissue damage[6]. It was not until 1968 that the first three cases of HO were described in patients with brain injuries[7]. In this study we focused on HO following neurological injuries, neurogenic heterotopic ossification (NHO), which usually affects major synovial joints that are surrounded by spastic muscles[2]. NHO occurs most often in patients with traumatic brain injury (TBI) and traumatic spinal cord injury (TSCI)[8,9], but can also be associated with other causes of upper motor neurone lesions such as stroke[2]. NHO typically develops within two to four months from neurological insult and manifests itself clinically as severe pain, swelling, erythema, warmth and decreased range of movement[10]. Patients with NHO usually develop lesions around larger joints, the hip being the most common location, followed by the knees and elbows[11]. A single joint is affected in ~40% of patients; in another third, two joints are affected[3]. Following its initial clinical manifestation, NHO tends to increase in size over the next few months and is usually fully developed two years post neurological injury[12].

The prevalence of NHO in TSCI patients has been estimated to be between 10% and 53%[13]. In TBI patients the prevalence of NHO has been reported as being between 10% and 20%[1,10,14]. More recent estimates have reported the prevalence

The authors have no conflict of interest.

Corresponding author: J.E Reznik, POB 165, James Cook University, QLD 4811, Australia
E-mail: jackie.reznik@jcu.edu.au

Edited by: S. Warden
Accepted 17 December 2013

Risk factors in development of NHO in traumatic spinal cord injuries			
Risk Factors	**Goldman, 1980**	**Coelho & Beraldo, 2009**	***Reznik et al, 2013**
Gender	M	M	M>F
Age	20-40	Not documented	31.4±10.9 years
Level of Injury	Thoracic lesion	Thoracic lesion	Not significant
Complete/Incomplete	**Complete	**Complete	***AIS B
Spasticity	Absent/Mild	Absent/Mild	Not significant
Pressure Ulcers	Present	Present	Multiple pressure ulcers
DVT	No	No	Significant
Length of Stay	>6 weeks	Not documented	207±175 days
Type of injury	RTA	Not documented	RTA
Smoking	Not documented	No	Not significant
Urinary complications	Not documented	Present	Significant
M=Male; F= Female; AIS = ASIA Impairment Scale; RTA= Road Traffic Accident **unpublished data* ***As per Frankel Scale (Appendix 2)* **** see AIS Scale (Appendix 1)*			

Table 1. Risk factors for developing neurogenic heterotopic ossification.

Risk factors in development of NHO in traumatic head injuries			
Risk factors	**Simonsen, 2007**	**Van Kampen, 2011**	***Reznik et al, 2013**
Gender	M=F	M>F	M=100%
Age	Median 23 years	Median 35 years	39.6±15.5 years
Spasticity	Severe	Absent/mild	Severe
Length of Stay	Median 192 days	Not documented	143±117 days
Immobilisation	Yes	Not significant	Not documented
SAP levels	Raised	Not documented	Not documented
Mechanical ventilation	Not documented	Mean 16.50 days	Significant
Autonomic dysregulation	Not documented	Significant	Not documented
Long bone fractures	Not documented	Not significant	Significant
M=Male; F= Female; SAP= Serum Alkaline Phosphate **unpublished data*			

Table 2. Risk factors for developing neurogenic heterotopic ossification.

of NHO in TBI patients to be between 10% and 23% and 40-50% in SCI populations[15]. All recent figures of NHO prevalence are notably higher than previous estimates of ~3% and 4% for TBI and TSCI patients, respectively, as described in the early 60s and 80s of the last century[16,17]. It is of interest to note that the prevalence of NHO after TSCI is lower in paediatric patients than in adults, and spontaneous resorption of the neurogenic HO has been reported in children[18].

Many risk factors for NHO have been identified; most of them, however, do not appear to have a clear biological basis, evidenced by a weak association with the disease. These include vascular stasis, oedema, and prolonged swelling, as possibly contributing to NHO formation[19,20]. Demographic factors such as age, gender and ethnicity have also been suggested to increase the risk of NHO[9]. Some clinical characteristics and factors associated with the clinical management of traumatic neurological injuries such as length of time in coma, and artificial ventilation in patients with TBI[6], as well as completeness and level of spinal cord injuries in TSCI patients, have been suggested to heighten the risk of NHO[14,17]. Marked spasticity, length of time before being admitted to a specialised unit, associated fractures at the time of injury, pressure ulcers and uri-

nary tract infections have also been suggested as possible risk factors in the development of NHO[21].

In order to identify patients with a high-level risk for NHO after traumatic brain and spinal cord injuries, an audit was conducted of patients admitted to specialised units at the Hampstead Rehabilitation Centre in Adelaide, Australia.

Materials and methods

Ethics approval was granted by the Royal Adelaide Hospital Human Research Ethics Committee (RAH PROTOCOL NO: 121124).

Identification of patients

TBI and TSCI patients were identified using the Open Architecture Clinical Information System used at the Hampstead Rehabilitation Centre (OACIS). This OACIS system enables data to be gathered from different clinical systems and uploaded into a central repository. The separation summaries and clinical reports of all patients admitted to the Spinal Injury Unit and Brain Injury Unit at the Hampstead Rehabilitation Centre in Adelaide, Australia, between January 2007 and December 2012, were identified.

The diagnosis of NHO in TBI and TSCI patients was made only when NHO became a clinically significant condition. The screening protocol for TBI and TSCI patients admitted to the specialised units at HRC included physiotherapy assessments and medical imaging.

Physiotherapy assessments as per standard care included:

a) Measures of passive range of motion (ROM) in upper limbs (UL) and lower limbs (LL) performed uni- laterally and bilaterally at a minimum of weekly intervals.
b) Recorded or self-reported measures of spasticity in terms of mild, moderate or severe (UL, LL, truncal).

The presence of one or more of the following signs indicated the possibility that NHO was present:

1) an objective decrease of more than 5 arc degrees (°) in passive ROM from previous assessment;
2) an increase in severity of spasticity from the previous assessment;
3) inflammatory signs at the hip/pelvis such as redness, heat, and swelling;
4) abnormal joint "end feel" on passive ranging (flexion/abduction hip).

Clinical suspicion of NHO i.e. the presence of one or more of the above signs and symptoms was confirmed or excluded by radiography using the technetium whole body bone scan[11].

Audit protocol

We adopted the audit protocol originally developed by Goldman (1980) and modified according to more recently published literature[6,10,13,15]. The audit itself was conducted between February and August 2013 and clinically relevant characteristics, as previously identified from the literature, were manually extracted and recorded in a Microsoft Excel spread sheet. Where information was missing or sparse the treating physician or physiotherapist was consulted. The list of all variables recorded is shown in Supplementary Table 1. Recorded data were subsequently statistically analysed to identify TBI and TSCI patients at high risk of developing NHO. A priori risk factors in the development of NHO in TSCI and TBI respectively, are as documented in Tables 1 and 2.

Statistical analysis

Univariate association of continuous and nominal covariates with NHO was examined by Mann-Whitney U test and Fisher's exact test, respectively. Our binary outcome was the presence of NHO in patients with TBI or TSCI. Logistic regression was used to model the effects of multiple covariates on binary outcome and results were presented as odds ratio (OR) with its 95% confidence interval (95% CI). Statistical significance was defined at the conventional 5% level. All computations were performed using the SPSS statistical package v.20.0.0.

Results

The OACIS tool identified 262 TBI patients, 151 TSCI patients, and 11 patients with a combined head and spinal cord injury admitted to the Hampstead Rehabilitation Centre between January 1 2007 and December 31 2012. The latter 11 patients were considered to be confounders and were removed from further analyses. NHO was diagnosed in 10 and 16 patients with TBI and TSCI, respectively (Supplementary Table 1). Eighteen clinically relevant characteristics were recorded and analysed for the association with NHO in TBI and TSCI patients (Supplementary Table 1).

Mode of injury in patients with TBI and TSCI

The most common modes of injury, accounting for more than 50% of all identified TBI and TSCI patients, were falls (TBI=23.66%, TSCI=18.54%), driver or passenger motor vehicle accidents (TBI=22.90%, TSCI=27.81%), and motorbike accidents (TBI=17.89%, TSCI=18.54%), (Figure 1). TBI, compared to TSCI, was significantly more associated with assaults (15.64% vs. 0.66%, P<0.001) and pedestrian accidents (8.78% vs. 0.66%, P<0.001). On the other hand TSCI as compared to TBI was significantly more associated with sporting accidents (TSCI=11.92%, TBI=1.91%, P<0.001), industrial or work related accidents (TSCI=5.96%, TBI=0.00%, P<0.001), and accidents associated with flying activities (TSCI=2.65%, TBI=0.00%, P=0.017) (Figure 1).

Diagnosis of NHO in patients with TBI and TSCI

NHO was diagnosed by radiography using the technetium whole body bone scan[11], when it became clinically significant. All TBI and TSCI patients who developed clinically significant NHO had decreased ROM at the affected joint by at least 5°.

Sites of NHO in patients with TBI and TSCI

Both groups developed NHO most commonly in the hip joint. The elbow was involved significantly more often in TBI

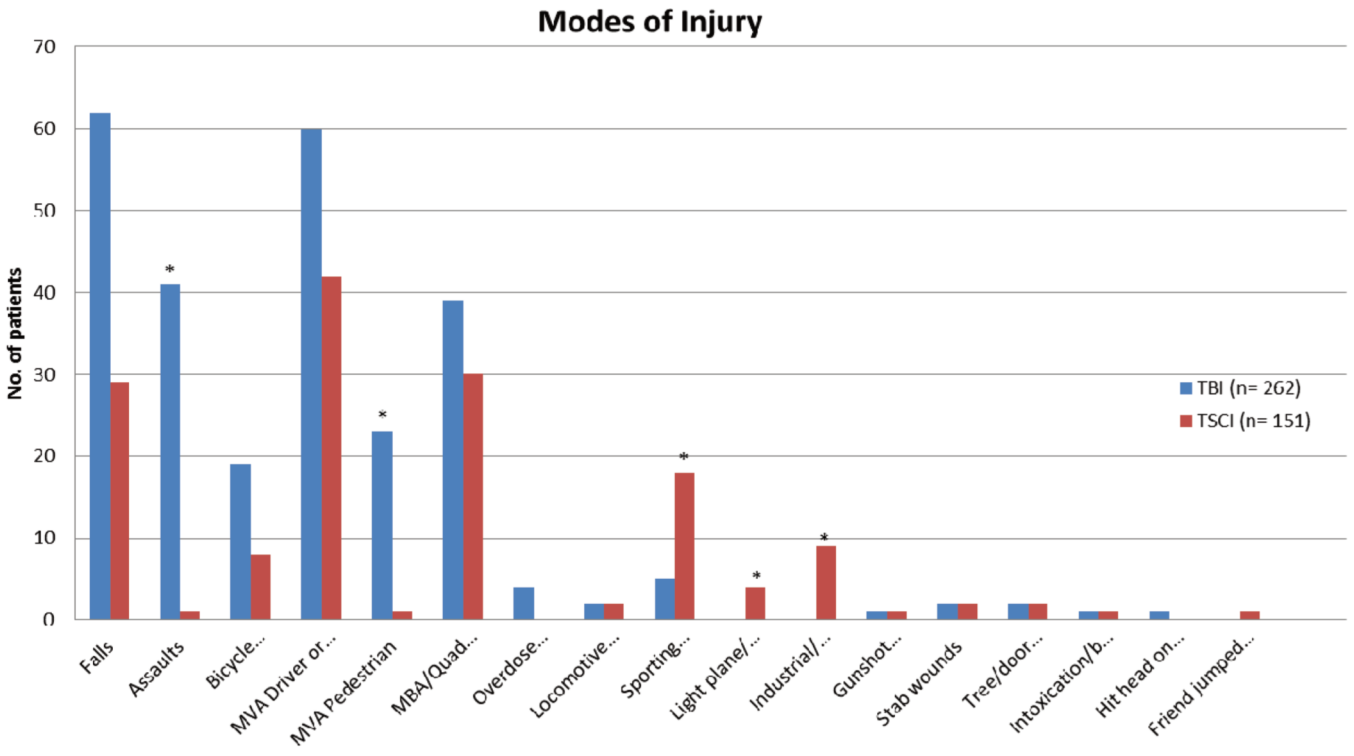

Figure 1. Bar graph showing the numbers of patients with TBI and TSCI according to the mode of injury. *(TBI= Traumatic Brain Injury; TSCI= Traumatic Spinal Cord Injury; MVA= motor vehicle accident; MBA= Motorbike accident; n= number of patients; *statistically significant difference).*

Joint		TBI-HO (n=10*)	TSCI-HO (n=16*)	P
Shoulder	Unilateral	0 (0%)	0 (0%)	-
	Bilateral	0 (0%)	1 (6%)	>0.999
Elbow	Unilateral	3 (30%)	0 (0%)	0.046
	Bilateral	0 (0%)	0 (0%)	-
Hip	Unilateral	4 (40%)	10 (63%)	0.301
	Bilateral	0 (0%)	3 (19%)	0.215
Knee	Unilateral	3 (30%)	1 (6%)	0.157
	Bilateral	0 (0%)	1 (6%)	>0.999

*NHO= Neurogenic Heterotopic Ossification; TBI-HO= Traumatic Brain Injury with Heterotopic Ossification; TSCI-HO= Traumatic Spinal Cord Injury with Heterotopic Ossification; *n = number of patient with clinically significant NHO (some patients had more than one site affected).*

Table 3. Sites of NHO.

patients than TSCI patients (Table 3).

With regards to the sites of NHO, elbows were unilaterally affected in TBI patients rather than TSCI patients (30% vs. 0%, P=0.046; Table 3). However, NHO developed unilaterally more often in the hip area in TSCI patients than TBI patients (63% vs. 40%), though the difference did not reach statistical significance (P=0.301; Table 3).

Risk factors associated with NHO in patients with TBI and TSCI

We performed the analysis of clinically relevant variables in TBI and TSCI patients to assess their association with NHO. We found that the prevalence of NHO in TBI patients was about one-third of that found in TSCI patients, 4% and 11%, respectively (Table 4). The only variables that appeared to be commonly associated with NHO in both neurological conditions

Table 4. Univariate analysis of patients with and without NHO after traumatic brain and spinal cord injuries *(continuous on the next page)*.

Characteristic		**TBI**			**TSCI**		
		NHO	**No NHO**	**P**	**NHO**	**No NHO**	**P**
N		**10 (4%)***	**252 (96%)**	**-**	**16 (11%)***	**135 (89%)**	**-**
Age (years)		39.6±15.5	39.9±16.2	0.852	31.4±10.9	38.1±17.5	0.288
Male		10 (100%)	216 (86%)	0.366	13 (81%)	115 (85%)	0.713
Female		0 (0%)	36 (14%)	0.366	3 (19%)	20 (15%)	0.713
ISNCSCI level	Cervical	-	-	-	11 (69%)	68 (50%)	0.177
	Thoracic	-	-	-	5 (31%)	49 (36%)	0.715
	Lumbar	-	-	-	0 (0%)	10 (7%)	0.314
	Cauda Equina	-	-	-	0 (0%)	8 (6%)	0.399
AIS score	A	-	-	-	8 (50%)	53 (39%)	0.422
	B	-	-	-	**6 (38%)**	**16 (12%)**	**0.017**
	C	-	-	-	1 (6%)	19 (14%)	0.430
	D	-	-	-	**1 (6%)**	**39 (29%)**	**0.046**
	E	-	-	-	0 (0%)	1 (1%)	0.894
	Central cord lesion	-	-	-	0 (0%)	5 (4%)	0.567
	Hemi-section of cord	-	-	-	0 (0%)	2 (1%)	0.799
Lowest GCS at time of injury	Nil/not noted	2 (20%)	63 (25%)	0.773	-	-	-
	Mild	2 (20%)	59 (23%)	0.857	-	-	-
	Moderate	0 (0%)	44 (18%)	0.154	-	-	-
	Severe	6 (60%)	86 (34%)	0.116	-	-	-
Length of PTA (days)	No	4 (40%)	121 (48%)	0.640	-	-	-
	Mild	0 (0%)	0 (0%)	-	-	-	-
	Moderate	0 (0%)	3 (1%)	0.889	-	-	-
	Severe	0 (0%)	14 (6%)	0.572	-	-	-
	Very severe	6 (60%)	114 (45%)	0.382	-	-	-
Period of Intubation (days)	<1	0 (0%)	19 (7%)	>0.999	-	-	-
	2-5	0 (0%)	17 (7%)	>0.999	-	-	-
	6-10	0 (0%)	11 (4%)	>0.999	-	-	-
	11-15	0 (0%)	4 (1%)	>0.999	-	-	-
	16-25	1 (10%)	9 (4%)	0.327	-	-	-
	>25	**3 (30%)**	**7 (3%)**	**0.004**	-	-	-
	Unknown	4 (40%)	57 (23%)	0.245	-	-	-
	Not noted	2 (20%)	128 (51%)	0.103	-	-	-
Spasticity		**5 (50%)**	**9 (4%)**	**<0.001**	10 (63%)	65 (48%)	0.303
Level of intoxication		0 (0%)	18 (7%)	>0.999	-	-	-
Urinary tract infections		**3 (30%)**	**23 (9%)**	**0.065**	13 (81%)	78 (58%)	0.104
Albumin (g/L)		35.1±3.7	36.1±4.5	0.387	33.9±2.8	33.2±4.8	0.549
WCC (10^9/L)		8.0±3.4	7.8±2.8	0.556	7.9±2.7	8.1±2.8	0.823
DVT/PE		**4 (40%)**	**16 (6%)**	**0.004**	**4 (25%)**	**8 (6%)**	**0.025**
Pressure Ulcers	Pre-pressure areas	-	-	-	0 (0%)	2 (2%)	>0.999
	Heels/malleoli	1 (10%)	4 (2%)	0.178	0 (0%)	6 (4%)	>0.999
	Sacral area/buttocks	0 (0%)	3 (1%)	>0.999	4 (25%)	13 (10%)	0.085
	Ischial tuberosity	-	-	-	1 (6%)	6 (4%)	0.551
	Multiple pressure ulcers	-	-	-	**5 (31%)**	**9 (7%)**	**0.008**
	Miscellaneous (ear)	0 (0%)	1 (1%)	>0.999	-	-	-
	High risk but not noted	1 (10%)	3 (1%)	0.145	-	-	-
	Nil noted	8 (80%)	241 (95%)	0.082	6 (38%)	99 (73%)	0.007
	Pre-pressure areas	-	-	-	0 (0%)	2 (2%)	>0.999

Table 4. *(continued from previous page).*

Characteristic		TBI			TSCI		
		NHO	**No NHO**	**P**	**NHO**	**No NHO**	**P**
Length of stay		**143±117**	**54.7±16.2**	**<0.001**	207±175	122±113	0.055
Smokers/ non smokers		1 (10%)	32 (13%)	>0.999	5 (31%)	26 (19%)	0.324
Associated Injuries	**Multiple injuries**	**6 (60%)**	**59 (23%)**	**0.017**	2 (13%)	11 (8%)	0.631
	Spinal dislocation	-	-	-	13 (81%)	78 (58%)	0.104
Co-morbidities							
Asthma		0 (0%)	5 (2%)	>0.999	0 (0%)	9 (7%)	0.598
Cardiovascular disorders		0 (0%)	7 (3%)	>0.999	0 0(%)	4 (3%)	>0.999
Orthopaedic disorders		1 (10%)	5 (2%)	0.210	1 (6%)	14 (10%)	>0.999
Systemic disorders		1 (10%)	10 (4%)	0.354	1 (6%)	7 (5%)	>0.999
Chronic pain		0 (0%)	2 (1%)	>0.999	0 (0%)	2 (1%)	>0.999
Psychiatric disorders		2 (20%)	17 (7%)	0.158	0 (0%)	3 (2%)	>0.999
Alcoholism		0 (0%)	20 (8%)	>0.999	0 (0%)	3 (2%)	>0.999
Miscellaneous co-morbidities		1 (10%)	8 (3%)	0.299	0 (0%)	14 (10%)	0.364
CCI		0.6±0.9	0.3±0.7	0.175	0.2±0.4	0.5±0.8	0.410

TBI – Traumatic brain injury *TSCI – Traumatic spinal cord injury*
NHO – Neurogenic heterotopic ossification *ASIA – American Spinal Injuries Association*
ISNCSCI – International Standard for Neurological Classification of Spinal Cord Injury
AIS – ASIA Impairment scale *PTA – Post-traumatic amnesia*
GCS – Glasgow coma scale *PE – Pulmonary embolus*
DVT – Deep vein thrombosis
CCI – Age-adjusted Charlson Comorbidity Index *WCC – White Cell Count*
Nominal variables are presented as numbers; continuous variables are presented as mean ± standard deviation. Continuous and nominal variables were compared between subjects with and without NHO using Mann Whitney U test and Fisher's exact test, respectively.
Reference: *Charlson ME, Pompei P, Ales KA, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases. 1987;40(5):373-83.*

Risk factor	TBI			TSCI		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Spasticity	27.75	6.40-120.27	<0.001	-	-	-
Period of intubation (>25 days)	18.73	3.64-96.24	<0.001	-	-	-
Urinary tract infections	6.74	1.55-29.27	0.011	-	-	-
Multiple injuries	5.70	1.54-21.07	0.009	-	-	-
Length of stay	1.00	1.00-1.01	0.120	-	-	-
Multiple pressure ulcers	-	-	-	5.61	1.55-20.30	0.009
AIS score B	-	-	-	3.59	1.09-11.79	0.035
AIS score D	-	-	-	0.20	0.02-1.65	0.136

TBI - Traumatic brain injury *TSCI – Traumatic spinal cord injury*
DVT – Deep vein thrombosis *AIS –ASIA Impairment scale*
PE - Pulmonary embolus
OR, odds ratio; CI, 95% confidence intervals; P, P-value.
The association between individual risk factors and NHO was adjusted for age and gender.

Table 5. Multivariate association of risk factors with NHO in patients with traumatic brain and spinal cord injuries.

were deep vein thrombosis and/or pulmonary emboli (DVT/PE). The prevalence of DVT/PE in TBI patients with NHO was 40% compared to 6% in TBI patients without NHO (P=0.004). The prevalence of DVT/PE in TSCI patients with and without NHO was 25% and 6%, respectively (P=0.025; Table 4). Certain variables appeared to be exclusively associated with NHO in TBI or TSCI patients. In the TBI group of patients these include spasticity, period of intubation, urinary tract infections, multiple injuries and the length of stay (Table 4). In the TSCI group, patients with NHO, compared to patients without NHO, showed a significantly higher prevalence of multiple pressure ulcers and AIS B (ASIA Impairment Scale, Appendix 1) (Table 4). It should be noted however, that TSCI patients (AIS D) with NHO as compared to patients without NHO (i.e. sensory and motor incomplete), showed significantly less prevalence of NHO (Table 4). Adjusting for age and gender, DVT/PE remained a common predictor of NHO in both TBI patients (OR=10.35, 95% CI=2.51-43.63, P=0.001) and TSCI patients (OR=5.57, 95% CI=1.41-21.98, P=0.014) using logistic regression analysis (Table 5). Spasticity (OR=27.75, 95% CI=6.40-120.27, P<0.001) followed by the period of intubation >25 days (OR=18.73, 95% CI=3.64-96.24, P<0.001) urinary tract infection (OR=6.74, 95% CI=1.55-29.27, P=0.011) and multiple injuries (OR=5.70, 95% CI=1.54-21.07, P=0.009) were identified as predictors of NHO in TBI patients using logistic regression analysis (Table 5). Similarly, multiple pressure ulcers (OR=5.61, 95% CI=1.55-20.30, P=0.009) and AIS score B (OR=3.59, 95% CI=1.09-11.79, P=0.035) were predictors of NHO in TSCI patients using logistic regression analysis (Table 5).

Discussion

In the current study we screened a group of 413 patients with traumatic brain and spinal cord injuries for the presence of NHO. Our findings provide evidence that prevalence of NHO in TBI patients is less than one-third of that found in TSCI patients, in particular accounting for ~4% and 11%, respectively. These findings are similar to older estimates of NHO prevalence being about 3% and 4% in TBI and TSCI patients, respectively[16,17]. More recently published figures, however, are at least five-times higher in both neurological conditions[15]. The prevalence of NHO varies widely among institutions, as some specialised units screen for NHO routinely while others report only clinically significant NHO cases[21]. This might contribute to our relatively conservative estimates of NHO prevalence in TBI and TSCI patients as some of the most prominent complications of NHO, such as joint ankylosis, manifest themselves only in small number of patients[22].

The most notable finding from this study was that the risk factors associated with NHO in TBI and TSCI patients were almost completely distinct, suggesting that clinically significant NHO following traumatic brain and spinal cord injuries are clearly separate entities in terms of their associated risk factors. In addition we found an increase in the number of deep vein thromboses (DVT) prior to the diagnosis of NHO among the TBI and TSCI patients who subsequently developed NHO.

DVT remained the only common risk factor for NHO in these patients even after adjustment for other clinically relevant variables such as age and gender. This is expected as both TBI and TSCI patients often present with a number of additional risk factors associated with DVT development, including major surgery, fractures of the pelvis, hip, or long bones, and trauma, all of which can stimulate the levels of thrombogenic factors, such as factor III or thromboplastin, within the circulation[23]. Current understanding of the NHO pathogenesis supports the idea that multiple factors are crucial for its initiation and progression rather than a single risk factor such as DVT[15]. Indeed, approximately half of our TBI and TSCI patients who developed NHO had no symptoms of DVT. In descending order, according to the effect size, TBI patients with spasticity, period of intubation greater than 25 days, urinary tract infections, and multiple injuries had a higher risk of developing NHO. Most of these risk factors have been previously reported to be associated with NHO[21]; however, prolonged endotracheal intubation may represent a novel risk factor for NHO in TBI patients. A similar but more invasive surgically based ventilation technique, a tracheostomy, was previously associated with increased risk of NHO in TSCI but not TBI patients[21]. This was not the case in our TSCI group, where patients with multiple pressure ulcers, and AIS score B had the highest risk of developing NHO. One of the most important orthopaedic concerns for NHO is its ability to impair the mobility of sufferers. In this context, the functional significance of incomplete lesions as a risk factor for NHO is arguable, since mobility is already severely limited in this group of patients[24].

There are many reasons why risk factors for NHO are distinct in TBI and TSCI patients. It is possible that the mode of injury may contribute to the mechanisms of NHO formation, as the causes of upper motor neurone lesions were considerably different in TBI and TSCI patients. The prevalence of assaults and pedestrian motor vehicle accidents was significantly higher in traumatic brain injury cases, whereas sporting, flying, and industrial accidents appeared to be significantly more prevalent in patients with spinal cord injuries. These causes of TSCI frequently lead to prolonged or chronic physical impairements associated with the pressure ulcers[25], a recognized risk factor for NHO in TSCI patients[21]. Pressure ulcers also had the highest effect size in this study. On the other hand, assaults to the head often result in an increase in muscle activity and spasticity[26]; spasticity is a recognized risk factor for NHO in TBI patients[21].

NHO is found predominantly in the larger joints such as hips, knees, shoulders, and elbows[3,11]. In the current study we found that NHO predominantly developed in the elbow of TBI rather than TSCI patients. The exact mechanism for this finding is not evident in the current study; however TBI patients significantly differed from those with TSCI in terms of their risk factors for NHO development, including the level of spasticity. Thus it is reasonable to suggest that upper limb spasticity, associated with mechanical stress to the musculotendinous junction at the elbow joint, due to handling, might account for the relatively higher number of TBI patients who developed NHO around the elbow. This hypothesis is supported by pre-

vious findings that micro trauma may induce ossification through induction of local inflammatory responses or by releasing osteoblast-stimulating factors[27].

Finally, we also assessed some circulating inflammatory markers such as serum albumin and white blood cell count in TBI and TSCI patients. We found that patients with and without NHO had similar levels of these blood-borne indicators of systemic inflammation. This is in accord with previous findings which provides evidence that the use of common antiinflammatory agents, such as indomethacin, ibuprofen and aspirin, has only limited effectiveness in the pharmacological management of NHO[10]. Thus some other clinical interventions such as the extracorporeal shock wave therapy (ESWT) could be investigated for their effectiveness in these patients[28,29].

The current study has several limitations; in order to minimize some of the difficulties in identifying patients, the study was conducted at specialised brain injury and spinal cord injury units at one rehabilitation centre that implemented the OACIS system. This tool allows for gathering relevant clinical data and patients characteristics in a very uniform, precise manner. As a result of this design, NHO was identified only when it was a clinically significant condition, thus the number of TBI and TSCI patients with NHO was relatively small which may limit the statistical power, and the number of risk factors identified in the study. This study, however, was a retrospective audit, and the findings need to be confirmed in a large prospective study. A further limitation was that the majority of available TBI and TSCI patients were male, limiting the relevance of our findings to NHO in women. Finally, it must be noted that the period of intubation for the TSCI patients was not available using the OACIS tool, and might be useful information to have in future studies.

In conclusion, this study suggests that the risk factors associated with NHO in TBI patients are distinct from those identified in TSCI patients. Our findings may have practical implications in the clinical management of patients with NHO following traumatic neurological injuries.

Acknowledgements

The authors would like to thank the staff at Hampstead Rehabilitation Centre for their cooperation in collecting the data.

References

1. Bossche LV, Vanderstraeten G. Heterotopic ossification: A review. Journal of Rehabilitation Medicine 2005; 37:129-36.
2. McCarthy EF, Sundaram M. Heterotopic ossification: A review. Skeletal Radiology 2005;34:609-19.
3. Simonsen LL, Sonne-Holm S, Krasheninnikoff M, Engberg AW. Symptomatic heterotopic ossification after very severe traumatic brain injury in 114 patients: Incidence and risk factors. Injury 2007;38:1146-50.
4. Geschickter C, Maseritz I. Myositis Ossificans. J Bone Joint Surg Am 1938;20:661-74.
5. Dejerine Y, Ceillier A. Para-osteo-arthropathies des paraplegiques par lesion medullaire: Etude anatomique et histologique. Rev Neurol 1919;32:399-407.
6. Van Kampen PJ, Martina JD, Vos PE, Hoedemaekers CWE, Hendricks HT. Potential risk factors for developing heterotopic ossification in patients with severe traumatic brain injury. Journal of Head Trauma Rehabilitation 2011;26:384-91.
7. Roberts PH. Heterotopic ossification complicating paralysis of intracranial origin. J Bone Joint Surg 1968; 50B:70-7.
8. Chalidis B, Stengel D, Giannoudis PV. Early excision and late excision of heterotopic ossification after traumatic brain injury are equivalent: A systematic review of the literature. Journal of Neurotrauma 2007;24:1675-86.
9. Van Kuijk AA, Geurts ACH, Van Kuppevelt HJM. Neurogenic heterotopic ossification in spinal cord injury. Spinal Cord 2002;40:313-26.
10. Cipriano CA, Pill SG, Keenan MA. Heterotopic ossification following traumatic brain injury and spinal cord injury. Journal of the American Academy of Orthopaedic Surgeons. 2009;17:689-97.
11. Seipel R, Langner S, Platz T, Lippa M, Kuehn JP, Hosten N. Neurogenic heterotopic ossification: epidemiology and morphology on conventional radiographs in an early neurological rehabilitation population. Skeletal Radiology 2012;41:61-6.
12. Garland DE. A clinical perspective on common forms of acquired heterotopic ossification. Clinical Orthopaedics and Related Research 1991;263:13-29.
13. Teasell RW, Mehta S, Aubut JL, Ashe MC, Sequeira K, MacAluso S, et al. A systematic review of the therapeutic interventions for heterotopic ossification after spinal cord injury. Spinal Cord 2010;48:512-21.
14. Coelho CVC, Beraldo PSS. Risk factors of heterotopic ossification in traumatic spinal cord injury. Arquivos de Neuro-Psiquiatria 2009;67:382-7.
15. Sakellariou VI, Grigoriou E, Mavrogenis AF, Soucacos PN, Papagelopoulos PJ. Heterotopic ossification following traumatic brain injury and spinal cord injury: Insight into the etiology and pathophysiology. J Musculoskelet Neuronal Interact 2012;12:230-40.
16. Damanski M. Heterotopic ossification in paraplegia. J Bone Joint Surg 1961;43:286-99.
17. Goldman J. Heterotopic ossification in spinal cord injuries. Physiotherapy 1980;66:219-20.
18. Hitzig SL, Tonack M, Campbell KA, McGillivray CF, Boschen KA, Richards K, et al. Secondary health complications in an aging Canadian spinal cord injury sample. Am J Phys Med Rehabil 2008;87:545-55.
19. Beilby J, Mulligan H. Deep vein thrombosis and heterotopic ossification following spinal cord injury - a clinical perspective for physiotherapists. New Zealand Journal of Physiotherapy 2008;36:7-14.
20. Bradleigh LH, Perkash A, Linder SH, Sullivan GH, Bhatt HK, Perkash I. Deep venous thrombosis associated with

heterotopic ossification. Arch Phys Med Rehabil 1992; 73:293-4.
21. Citak M, Suero EM, Backhaus M, Aach M, Godry H, Meindle R, Schildhauer TA. Risk Factors for Heterotopic Ossification in Patients with Spinal Cord Injury. Spine 2012;37:1953-7.
22. Mavrogenis AF, Soucacos PN, Papagelopoulos PJ. Heterotopic ossification revisited. Orthopedics 2011;34:177.
23. Martinelli I, Bucciarelli P, Mannucci PM. Thrombotic risk factors: Basic pathophysiology. Crit Care Med 2010; 38:S3-9.
24. Kirshblum SC, Waring W, Biering-Sorensen F, Burns SP, Johansen M, Schmidt-Read M, Donovan W, Graves D, Jha A, Jones L, Mulcahey MJ, Krassioukov A. Reference for the 2011 revision of the International Standards for Neurological Classification of Spinal Cord Injury. J Spinal Cord Med 2011;34:547-54.
25. Lyder CH. Pressure ulcer prevention and management. JAMA 2003;289:223-6.
26. Wright DW, Kellermann A, McGuire LC, Chen B, Popovic T. CDC grand rounds: Reducing severe traumatic brain injury in the United States. MMWR 2013; 62:549-52.
27. Silver JR, Heterotopic ossification. A clinical study of its possible relationship to trauma. Paraplegia 1969;7:220-230.
28. Reznik JE, Gordon SJ, Barker RN, Keren O, Arama Y, Galea MP. Extracorporeal Shock Wave Therapy (ESWT) as a treatment for recurrent Neurogenic Heterotopic Ossification (NHO). Brain Inj 2013;27:242-7.
29. Reznik JE, Milanese S, Golledge J, Biros E, Galea MP. Extracorporeal shock wave therapy as a treatment for heterotopic ossification. PTR 2013;18:300-7.

Supplementary Table 1. Variables recorded.

Variable		**TBI**	**TSCI**
Patients (number)		262	151
NHO (number)		10	16
Combined (number)		11	
Date of injury		√	√
Age at time of injury		√	√
Gender		√	√
ISNCSCI		X	√
AIS		X	√
GCS		√	X
Length of time in PTA		√	X
Presence of NHO /number of joints affected		√	√
Presence of DVT/PE		√	√
Presence of UTI		√	√
Presence/ number of PU's		√	√
Presence of spasticity		√	√
Mechanical ventilation		√	X
Co - morbidities	Respiratory disorders	√	√
	Cardiovascular disorders	√	√
	Orthopaedic disorders	√	√
	Chronic pain	√	√
	Psychiatric disorders	√	√
	EtOH abuse	√	√
Length of stay in unit		√	√
Mode of separation		√	√
Nursing/Physiotherapy Management		√	√
Blood characteristics	Albumin (g/L)	√	√
	WCC (10^9/L)	√	√

ISNCSI - International Standard Neurological Classification of Spinal Cord Injury
DVT - Deep Vein Thrombosis
PE - Pulmonary Embolus
AIS - ASIA Impairment Scale
UTI - Urinary Tract Infection
GCS - Glasgow Coma Scale
PU - Pressure Ulcer
PTA - Post Traumatic Amnesia
EtOH - Ethanol Abuse
NHO - Neurogenic Heterotopic Ossification
WCC - White Cell Count

Appendix 1

Asia impairment scale

- 'A' being complete and having no sensory or motor function preserved in the sacral segments of S4 to S5.
- 'B', sensory incomplete, is having sensation but not motor function reserved below the neurological level and includes the sacral segments S4-S5 (light touch, pinprick, at S4-S5: or deep anal pressure (DAP)), and **no** motor function is preserved more than three levels below the motor level on either side of the body.
- 'C', motor incomplete, is motor function preserved below the neurological level, and more than half of the key muscle functions below the single neurological level of the injury (NLI) have a muscle grade of less than 3 (grades 0-2).
- 'D' is also motor incomplete and has motor function preserved below the neurological level, and at least half of the key muscle functions below the NLI have a muscle grade equal or greater than 3.
- 'E' is classified when sensation and motor function, as tested with the ISNCSCI, are graded as normal in all segments and the patient has had prior SCI deficits. (Someone without an initial SCI does not receive an AIS grade)

Reference: Kirshblum SC, Waring W, Biering-Sorensen F, Burns SP, Johansen M, Schmidt-Read M, Donovan W, Graves D, Jha A, Jones L, Mulcahey MJ, Krassioukov A. Reference for the 2011 revision of the International Standards for Neurological Classification of Spinal Cord Injury. J Spinal Cord Med 2011;34(6):547-54.

Appendix 2

Acute spinal cord injury - Frankel classification grading system

Grade A Complete neurological injury - no motor or sensory function clinically detected below the level of the injury.

Grade B Preserved sensation only - no motor function clinically detected below the level of the injury; sensory function remains below the level of the injury but may include only partial function (sacral sparing qualifies as preserved sensation).

Grade C Preserved motor non-functional - some motor function observed below the level of the injury, but is of no practical use to the patient.

Grade D Preserved motor function - useful motor function below the level of the injury; patient can move lower limbs and walk with or without aid, but does not have a normal gait or strength in all motor groups.

Grade E Normal motor - no clinically detected abnormality in motor or sensory function with normal sphincter function; abnormal reflexes and subjective sensory abnormalities may be present.

Reference: Donovan WH, Brown DJ, Ditunno JF Jr, Dollfus P, Frankel HL. Neurological issues. Spinal Cord 1997;35(5):275-81.