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The association between deep venous thrombosis and heterotopic ossification in patients with acute traumatic spinal cord injury

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The medical records of 209 patients with acute traumatic spinal cord injury (SCI) admitted to the SCI rehabilitation unit from 7/1/88 through 12/31/92 were reviewed. Whereas the incidence of heterotopic ossification (HO) and deep venous thrombosis (DVT) in this population were 16.7% and 14.3%, respectively, 36.6% of the individuals with DVT had HO. 31.4% of those with HO developed DVT at some time during their acute or rehabilitation hospitalization. The overall incidence of coexistent DVT and HO was 5.3%. The correlation between the occurrence of HO and DVT in this SCI population reached statistical significance ($X^2 = 9.97$; $p < 0.005$). The results of this study suggest that there exists an association between the occurrence of DVT and HO following traumatic SCI. We hypothesize that venous compression from expanding heterotopic bone can result in lower limb DVT following traumatic SCI.

Keywords: heterotopic ossification; deep venous thrombosis; spinal cord injury.

Introduction

Heterotopic ossification (HO) is a common complication following traumatic spinal cord injury (SCI). The incidence is variable and ranges from 16% to 53%.[1–6] The spectrum of clinical features varies from incidental findings observed on plain radiographs,[4,6,7] to significant restriction in joint motion or ankylosis.[4,6–10] Heterotopic bone has been associated with compression of nervous tissues,[11–17] painful arthroses,[18,19] pressure ulcerations,[11] and malignant transformation.[20] Acute HO often mimics the clinical features of deep venous thrombosis (DVT).[21,22]

Heterotopic bone can result in compression of vascular structures.[12] This complication has been reported following subarachnoid hemorrhage,[23] traumatic brain injury,[17] and spinal cord injury.[12,17,24–26] The limited number of case reports describing the coexistence of DVT and HO following traumatic SCI suggest that vascular compression by developing heterotopic bone is quite uncommon in this population. The present study was designed to review our experience with coexistent DVT and HO following acute traumatic SCI in an effort to determine the association, if any, of these two distinct clinical conditions.

Methods

The medical records of all patients with acute traumatic SCI admitted to the SCI rehabilitation unit at The Ohio State University during the period of 7/1/88 through 12/31/92 were respectively reviewed. All patients with acute traumatic SCI who developed DVT and/or HO during their acute rehabilitation hospitalization were included in the study. Demographic and injury data were collected, as well as any

information regarding the diagnosis of DVT and HO in these patients. Whenever DVT and HO coexisted in any patient, the chronological order of each diagnosis was determined. The chi squared test (X^2) was used to determine if there existed a significant relationship between the occurrence of DVT and HO in the population studied.

The criteria used for establishing the existence of DVT necessitated documentation of lower limb thrombosis by contrast venography, B-mode duplex ultrasonography, or both. The criteria used for determining the existence of HO necessitated documentation of heterotopic bone activity by three-phase bone scans or HO observed on plain radiographs. Alkaline phosphatase levels were not used in the determination of HO in this study.

All patients admitted to the SCI rehabilitation unit receive DVT prophylaxis in the form of compression stockings and low dose subcutaneous heparin unless contraindicated. Patients treated at our institution do not routinely receive prophylaxis against or screening for the presence of HO. However, all SCI patients are routinely screened for DVT by B-mode duplex ultrasonography upon admission to the rehabilitation unit. This technique can identify deep venous thrombosis as well as adjacent heterotopic bone,[22] although the effectiveness of this technique for diagnosing both conditions has not been extensively studied.

Results

Review of the medical records of all patients with acute traumatic SCI admitted to our SCI rehabilitation unit from 7/1/88 through 31/12/92 showed that the incidence of DVT and HO during the acute and rehabilitation hospitalization were 14.3% (30/209) and 16.7% (35/209), respectively. The age, sex, and neurological injury levels for all patients and those with HO and DVT are depicted in Table I. A larger number of patients with motor complete paraplegia and quadriplegia developed DVT and HO.

The incidence of coexistent DVT and HO was 5.3% (11/209). The etiologies for the injuries sustained in this group included eight motor vehicle accidents, two falls, and one gun shot wound. All patients had HO activity detected around the hip on the same side of the body as the diagnosed DVT; 7 patients had bilateral involvement by HO. In all cases, the acute DVT was diagnosed prior to detection of HO. Ten of the 11 patients with coexistent DVT and HO had their acute DVT diagnosed prior to the recognition of HO by an average of 29 days (range: 9–71 days). Coexistent DVT and HO were diagnosed within $3\frac{1}{2}$ months of

Table I Age at time of injury, sex, and neurological level for patients with DVT, HO, and coexistent DVT and HO

	Age[a] (years)	Sex (M/F)	Neurological level[b]	
			para	quad
DVT ($n = 30$)	30 (17–53)	27M/3F	13 PC 2 PI	13 QC 2 QI
HO ($n = 35$)	30 (15–77)	32M/3F	13 PC 0 PI	20 QC 2 QI
DVT + HO ($n = 11$)	28 (18–50)	10M/1F	7 PC 0 PI	4 QC 0 QI
Total ($n = 209$)	32.5 (15–78)	163M/46F	67 PC 34 PI	50 QC 58 QI

[a]Mean age; range of ages appears in parentheses.
[b]PI = Paraplegia, motor incomplete; PC = Paraplegia, motor complete; QI = Quadriplegia, motor incomplete; QC = Quadriplegia, motor complete.

acute injury in these 10 patients (range: 50–97 days). One patient was observed to have developed heterotopic bone 108 days following the diagnosis of DVT; both conditions were diagnosed within 150 days of injury. He was transferred to the SCI unit 166 days following his injury. 36.7% of the patients with DVT had heterotopic bone. 31.4% of those patients with HO developed DVT at some time during their hospitalization. The correlation between the occurrence of HO and DVT in this SCI population was statistically significant using the chi square test of independence ($X^2 = 9.97$; $p < 0.005$). A frequency table depicting this relationship appears in Figure 1.

Discussion

A statistically significant relationship existed between the occurrence of DVT and HO in the SCI population studied. Although the incidence of DVT and HO were 14.3% and 16.7%, respectively, greater than 36% of the patients with DVT had HO. Approximately 31% of those patients with HO developed DVT at some time during their acute or rehabilitation hospitalization. HO activity was present on the same side of the body affected by the lower limb DVT in all cases. Despite this relationship, no definitive conclusions regarding cause and effect can be drawn from this retrospective study. The highly variable incidence of DVT[27–29] and HO[1–6] following traumatic SCI makes evaluation of cause and effect difficult. A large, well designed, prospective study which longitudinally follows the development of both DVT and HO would be required to further clarify this correlation.

Nevertheless, it is intriguing to speculate why an association between DVT and HO exists. HO involving the hip most commonly occurs in line with the iliopsoas muscle,

		DVT: Yes	DVT: No	Total
HO	Yes	$n = 11$ (5.02)[a]	$n = 24$ (29.98)[a]	35
	No	$n = 19$ (24.98)[a]	$n = 155$ (149.02)[a]	174
	Total	30	179	209

Figure 1 Frequency table for occurrence of DVT, HO, and coexistence of DVT and HO in 209 patients with acute traumatic SCI. A statistically significant association between DVT and HO was observed in the study population using the chi square test ($X^2 = 9.97$; $p < 0.005$).
[a]Values in parentheses represent expected frequencies based upon the chi square test.

anterior and caudal to the hip joint; and along the medial aspect of the thigh in the region of the adductor musculature.[3,4,7,8] The intensity of the local edema as well as the expanding ectopic mass associated with HO can be significant, resulting in an increased risk for compression of vascular structures and formation of lower limb thrombus. During the first several weeks following traumatic SCI, patients are at greatest risk for the development of acute thromboembolic events.[28,29] Immature heterotopic bone would more than likely not be detected by plain radiographs when evaluation of possible DVT occurs within this acute period following injury. The diagnosis of a thromboembolic event would make further evaluation of HO less likely.

The hypothesis that expanding heterotopic bone with its concomitant inflammatory reaction might actually compress vascular structures is supported in the literature.[12,17,21,26] Orzel *et al*[21] demonstrated venous compression by HO confirmed by contrast venography in 2 patients. Haselkorn *et al*[25] subsequently reported coexistent DVT and HO in a patient with transverse myelitis. They suggested that soft tissue edema impaired venous return, and could have lead to the development of thrombosis. Following this account, Varghese *et al*[17] identified 2 additional patients with SCI in which femoral vein compression resulted from heterotopic ossification. Extensive venous thrombosis was present in one of the cases. A case was recently described involving a young quadriplegic patient with long-standing HO who developed venous compression as evidenced on venography;[12] positional changes allowed flow of contrast material during one of the studies. Intermittent compression of the venous system of the lower limb was associated with thrombosis of intramuscular collateral vessels. Anatomical support for compression of vascular structures is based upon observations during surgery of femoral and profunda vessels and the femoral nerve enveloped in ectopic bone.[4,12]

The observation that vitamin K-dependent proteins are involved both in coagulation and in bone formation lead Buschbacher *et al*[18] to hypothesize that warfarin might prevent the formation of HO. In a review of 227 cases of SCI they found that 15% of their patients were treated for thromboembolic events and an additional 15% developed HO. None of the patients treated with warfarin developed HO.[18] These findings certainly contrast with this study and most likely represent the differences in evaluation of suspected HO. None of their patients with DVT had follow up bone scans or radiographs to determine the coexistence of DVT and HO, and it is unclear if any had subsequent evaluation for clinically suspected HO.

Despite the high incidence of HO following injury to the spinal cord, compression of vascular structures by ectopic bone appears quite uncommon. The overall prevalence of coexistent DVT and HO in our study population was only 5.2%. The large level of inflammation and vascularity involved in developing ectopic bone more often mimics thrombophlebitis and other serious conditions such as cellulitis, septic arthritis, hemorrhage, and bony tumors.[6,7,10,21,30]

Several factors could account for the low prevalence of vascular compression observed in our retrospective study. HO is often self limited, with minimal residual impairment,[6,10] and is frequently observed incidentally on plain radiographs. Partial or intermittent compression of vascular structures such as described previously, might not result in the clinical findings of DVT. Progression of bone formation sufficient to compress nearby vascular structures resulting in clinically apparent features might result in ankylosis prior to vascular compromise. In cases where DVT is diagnosed, further evaluation of HO is less likely.

The 11 cases of coexistent DVT and HO observed following traumatic SCI in the present series complement four previous reports.[12,17,24,26] Although an additional 4 cases were identified,[17,21,25] 2 occurred following transverse myelitis.[17,25] Orzel *et al*[21] described 2 patients with venous compression due to heterotopic bone confirmed by contrast venography; it was unclear if the patients had SCI. We are unaware of any other reports of coexistent DVT and HO following acute traumatic SCI in the English literature.

The four case reports describing coexistent DVT and HO following traumatic SCI involve 2 patients with traumatic paraplegia[17,26] and 2 with traumatic quadriplegia.[12,24] In 3 of these, HO was observed at or about the time of the diagnosis of DVT.[12,17,24] In the fourth case, described by Yarkony *et al*[26], the diagnosis of HO was made 17 days after the diagnosis of DVT. Ten of the 11 patients from our series had an acute DVT diagnosed prior to the detection of HO by an average of 29 days (range: 9–71 days).

The relationship regarding the diagnosis of DVT and HO, and the time of each diagnosis is clear when the acuity of the patient is considered. When DVT and HO were diagnosed at or about the same time,[12,17,21] a period of at least 6 months had elapsed between injury and diagnosis. After such a period of time, developing heterotopic bone would be more easily recognized during any evaluation of DVT. In cases where a DVT was diagnosed during the initial acute or rehabilitation hospitalization,[26] there was a greater period of time between the diagnosis of DVT and that of HO. Ten of our 11 patients had the diagnosis of coexistent DVT and HO was confirmed within $3\frac{1}{2}$ months following acute SCI. The diagnosis of DVT during the acute hospitalization undoubtedly accounts for the greater time period seen between the diagnosis of DVT and HO in all of our patients. Once the diagnosis of a life-threatening complication such as DVT is established, further evaluation of possible coexisting ectopic bone is less likely. It is only when other clinical or laboratory features appear (eg alteration in joint mobility, persistent or recurrent lower limb swelling, elevated alkaline phosphatase, etc), that further evaluation commences. At the time of DVT detection, radiographs taken during venography showed no evidence of HO in all patients studied; confirmation of HO occurred more often with three-phase bone scanning. Three-phase bone scans usually show active HO 2–6 weeks prior to radiographic findings.[8,11,21,31]

Pulmonary emboli (PE) occurred in 4 of our spinal injured patients who had coexistent HO. Two of these patients were excluded from this series because they were unable to meet the inclusion criteria for documenting lower limb thrombosis. The limited number of documented pulmonary emboli occurring during the study period ($n = 12$) did not allow for independent analysis of the association between PE and HO. Without documented lower limb involvement, postulating an association between DVT and HO would be arduous at best. One of the 2 patients excluded from this series developed HO which was shown by pelvic CT scan to be compressing the femoral vein. Although venous duplex studies were negative for lower limb DVT, he shortly thereafter developed an acute PE. The PE occurred over 6 months after injury, long after the highest risk period for the development of this serious complication.[28,29] This case was previously reported.[12]

Conclusion

The results of the present study suggest that there is an association between the occurrence of DVT and HO following traumatic SCI. Longitudinal prospective studies are needed to further clarify this relationship.

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