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Mini Review

The Incidence and Characteristics of Heterotopic Ossification in Patients with Spinal Cord Injury

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Abstract

Objective: This is a retrospective study. Our aim was to analyze the characteristics of SCI patients with HO and the risk factors associated with HO formation.

Materials-Methods: Hospital records of the inpatient SCI patients, treated between 2011-2012 at our hospital, were analyzed and the ones with HO development were identified. The demographic and clinical characteristics (neurological level and severity of injury according to ASIA/ISCoS Standards and ASIA Impairment Scale (AIS) of the patients, HO localization, presence of spasticity were evaluated, descriptive statistics were used to analyze the results.

Results: Three hundred fifty five SCI patients' data were investigated and forty (11%) of them (77.5%, male and 22.5% female) were found to have HO. The mean age was 40.85±17.40 years; the median duration of the injury was 24 months. 42.5 % of the patients were tetraplegic, 57.5 % were paraplegic. Half of the patients had complete (AIS A n: 20) injury. Thirty two patients were traumatic and 8 were non-traumatic in etiology. The knee and hip joints were the most frequently affected joints (47.5% and 42.5% respectively). Spasticity was found in 34 patients (85%).

Conclusion: The incidence and localization of HO in this group were in correlation with the published reports. The knee and hip location of HO and traumatic etiology were found most frequently. However unlike previous reports HO was more frequent in paraplegic patients. The identification of characteristics of the SCI patients and risk factors associated with HO can help to reduce the incidence.

Introduction

HO is defined as the formation of mature, lamellar bone in non-osseous tissue, usually between the muscle and the joint capsule [1]. It is a frequent complication following central nervous system disorders (brain injuries, tumors, encephalitis, and spinal cord lesions), multiple injuries, hip surgery and burns [2]. Several factors, including prostaglandin E2, bone morphogenetic protein, and the inflammatory process, are believed to contribute to the development of HO [3]. HO has been classified according to the clinical setting, location of HO, and progressive or isolated occurrence into post-traumatic, non traumatic or neurogenic, and myositis or fibro dysplasia ossificans progressive [4]. Neurogenic Heterotopic Ossification (NHO) is a devastating complication of major central nervous system trauma seen in more than 20% of patients with traumatic brain injury and/or spinal cord injury, appearing in characteristic patterns around major joints [5].

The incidence of HO in SCI is between 16% and 53%, depending on the incidence reports from various Institutions. Clinically significant HO develops in about 20% of patients with a SCI [6,7]. Joint ankylosis, skin breakdown, peripheral nerve entrapment, deep vein thrombosis and pain are the complications of HO [8]. Therefore, prophylaxis or early treatment of HO is extremely important. Once the diagnosis of early HO is confirmed, passive range-of-motion exercises to maintain joint mobility are recommended [9].

There are no completely effective prophylactic measures. Oral indomethacin, and recently, cyclooxygenase-2 inhibitors, has been used for prevention of HO [10]. Prophylactic irradiation is another choice but has a potential risk of malignancy [10] bisphosphonates were the intervention with strongest supportive evidence once HO had developed [11]. Surgical excision may be indicated if HO is matured [5]. Several factors, including prostaglandin E2, bone morphogenetic protein, and the inflammatory process, are believed to contribute to the development of HO [3].

These pathophysiological factors are important for developing new treatment strategies. Winkler and col. studied impact of hypoxia on HO in human skeletal tissue and reported that BM-4 gene which is important for formation of HO was highly expressed in hypoxia and Wang and col. Found that blockade of Gi signaling of Tie2 cells reduced the formation of HO. Therefore blocking of Tie2

Table 1: Demographic and clinical characteristics of patients.

	Demographic characteristic features	Number of all patients (n=355)	percent among all patients	Number of the HO patients (n=40)	Percent Of the HO patients among 40 HO patients	p value
Gender	Female	135	38	9	22,5	0.032*
	Male	220	62	31	77,5	
Etiology	Traumatic	226	64	32	80	0.021*
	Nontraumatic	129	36	8	20	
Completeness of injury	Complete	124	35	20	50	<0.01*
	Incomplete	231	65	20	50	
Injury level	Cervical	118	33	17	42,5	0.08
	Thoracal	213	60	21	52,5	
	Lomber	24	7	2	5	
Spastisicty	Presence	249	70	34	85	0.092
	Absence	106	30	6	15	
Tetra/para	Tetraplegic	118	33	17	42.5	0.052
	Paraplegic	237	67	23	57.5	

*P<0.05

cells expressing may be used in treatment strategy. ATP hydrolyzing agent was reported as decreased HO formation by inhibiting the the classic BMP signaling Pathway [12,13].

In a review about immunologic contribution of HO, Macrophages express osteo-inductive and HO-associated signaling factors and depletion of macrophages by clodranete treatment redused the volume of HO. Mast cells and Chymokine signaling are also important for formation of HO [14]. Therefore biologics seem to a treatment options especially in early stage of HO.

In mice model, pathophysiology of neurological heterotopic ossification following spinal cord injury is studied in terms of substance p and macrophage factors. In that study Prophylactic inhibition of substance P provides partial benefit and prophylactic depletion of macrophages reduced NHO size by 90%, with complete prevention in some animals [15]. In another spinal cord injured mice model study Bone Marrow Protein 2 caused HO in mice with SCI but not in healthy mice [16].

The literature reported that alkaline phosphatase levels can- not be used to draw clinical conclusions about maturity or recurrence of HO [9,17] Three-phase nuclear bone scanning can be used to diagnosis in earl stage. Ultrasonography is also prior to radiographic evidence. And by Magnetic Resonance Imaging the HO is detected at 1first or second days when the symptoms begin. Near-Infrared Optical Imaging was studied in a murine model and found to be early and non invasive detection of HO [1,5]. Deep vein thrombosis is one of the important differential diagnosis [18]. Our aim was to investigate the characteristics of SCI patients with HO and the risk factors associated with HO formation.

Materials and Methods

It is a retrospective study. Data were collected from the hospital records of the inpatient SCI patients, rehabilitated between 2011-2012 in Istanbul Physical Medicine and Rehabilitation Training and Research Hospital. This is one of the two rehabilitation training and research hospital and it is a referral center for SCI in our country. The patients who passed their acute onset was referred to this centre and stayed at least 4 weeks. Three hundred fifty five patients were analyzed and the ones with HO development were identified. The demographic and clinical characteristics (neurological level and severity of injury according to ASIA/ISCOS Standards and ASIA Impairment Scale (AIS) of the patients were recorded. HO localization and presence of spasticity were evaluated. HO was diagnosed by x ray, MRI or three phase scintigraphy.

Descriptive statistics (mean, standart deviation, median and frequency) were used to determine demographic features. To analyze the difference between the medians of two data sets we used Mann Whitney U test.

Results

Three hundred fifty five SCI patients' data were investigated (M=220 F=135, mean age: 41.89±14.76 years). Eleven percentage (n=40) subjects experienced HO (77.5%, male and 22.5% female) were found to have HO. Males were more likely to experience HO than females; 31 male patients(14%) had HO of 220 male SCI patients and 9 (7%) of 135 female patients had HO (p=0.032). The mean age was 40.85±17.40 years; comparing the age of patients with HO and without HO there was not significant. The median duration of the injury was 24 months (3-192 months). 42.5 % of the patients were tetraplegic, 57.5 % were paraplegic (Table 1). Half of the patients with HO had complete (AIS A n: 20) injury (table 2). However 35% of all

Table 2: Demographic Percent of the HO of patients.

AIS	Number of all patients (n=355)	percent among all patients	number of the HO patients (n=40)	Percent of the HO patients among 40 HO patients
A	124	35	20	50
B	55	16	10	25
C	76	21	8	20
D	93	26	2	5

Table 3: Localization of heterotopic ossification.

	Percent	number
elbow	7,5	3
hip	42.5	17
knee	47.5	19

the patients had complete injury. Complete injury was significantly more frequent than incomplete injury in HO patients ($p<0.01$). And Incomplete D was significantly less frequent than other incomplete groups ($p<0.06$). Thirty two patients were traumatic and eight were non-traumatic in etiology. (Table 1) Traumatic etiology was also significantly frequent in patients with HO (p: 0.021). The knee and hip joints were the most frequently affected joints (47.5% and 42.5% respectively) (table 3). Spasticity was found in 34 patients (85% of patients with HO) (table 1). Seventy seven percent of all patients had spasticity. This was not significantly different between patients with HO and without HO.

Discussion

HO is an important complication of SCI and among patients with SCI, the incidence of HO is reported as 1 to 50% but most large (or contemporary) series have identified the incidence to be 20 to 30% [7,19] In this study the incidence was not investigated but prevalence of HO in our patients were 11% among SCI patients. Incidence is the rate of new (or newly diagnosed) cases of the disease. But we reported the patients who had already HO at charge or develop HO at the inpatient clinic.

The incidence of neurogenic HO after SCI is lower in pediatric patients than in adults, ranging from 3% to 10% [20]. There was only one patient younger than 18 years old in this study. The literature mentioned that there was significantly higher incidence in patients between 20 and 30 years old [6]. Our findings in terms of age were not like the literature, we did not find significant difference between patients with HO and without HO in terms of age: ($p=0.496$) in this study the beginning of the HO was not reported that could be the reason.

Gender dependence for neurogenic HO varies widely in the literature. Wittenberg and friends reported HO occurred more often in male patients (23%) than female (10%) patients [5]. In this study male patients (14%) were also more frequent than female patients (7%).

Heterotopic Ossification (HO) in spinal cord injury occurs commonly within the first 4 months of injury [21]. But the range was 2 weeks to 2-3 years after the injury in the literature [7,23]. In this study duration of injury varies between 3 months to 192 months .This was a limitation of the study.

The risk factors associated with the development of HO in patients with traumatic SCI has been studied in a case control study of 264 patients by Citak et al. According to this study, patients with spasticity and complete lesion had a higher risk of developing HO [20]. Krauss et al found significant correlation between AIS grade and HO [21]. In our study AIS A was significantly high frequent and AIS D was low frequent in patients with HO. In contrast the literature we found spasticity presence in patients with HO was not significantly different than patients without HO [22].

In SCI, HO always occurs below the level of the lesion, most commonly at the hip (70-97%) and knee, elbow and shoulder [23]. Like the literature knee and hip were was the most frequent site in our patients (47.5% and 42.5%) However knee HO was seen in 2 patients more than hip HO. The limitations of this study were that we could only define the HO patients during their charge in our inpatient clinic. This was a retrospective study that the injury durations varies as mentioned before. Prophlaxy history for HO before charge was not recorded.

However according to our knowledge there was not any study about the prevalence of HO in Turkish population. Even there were limitations to define the prevalence this was a suggestive study for HO.

Conclusion

The incidence and localization of HO in this group were in correlation with the published reports. The knee and hip location of HO and traumatic etiology were found most frequently. However unlike previous reports HO was more frequent in paraplegic patients. The identification of characteristics of the SCI patients and risk factors associated with HO can help to reduce the incidence.

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