J Orthopaed Traumatol (2002) 2:125–128
© Springer-Verlag 2002

ORIGINAL

G. Sessa
L. Costarella
R. Mollica
V. Pavone

Heterotopic ossification after total hip replacement and the HLA system in the Sicilian population

Received: 16 January 2002
Accepted: 18 February 2002

G. Sessa • L. Costarella • V. Pavone (✉)
Orthopaedics Clinic,
University of Catania,
Via Plebiscito 628, I-95124 Catania, Italy
Tel: +39-095-387802
Fax: +39-095-350611
E-mail: vitopavone@hotmail.com

R. Mollica
Orthopaedics Clinic,
Rehabilitation Section,
La Sapienza University, Rome, Italy

Abstract Heterotopic ossification (HO) is a frequent complication following total hip arthroplasty (THA). At present, the etiology of HO is unknown, however, genetic predisposition may be a cause of HO in individuals in whom no risk factors can be detected. The goal of this study was to investigate the HLA system, searching for any correlation with the presence of HO after THA. Thirty-five patients of Sicilian origin were operated on between January 1997 and January 1999 for cementless THA under regional anesthesia. The entire series was divided into three groups and all underwent histocompatibility typing. Group 1 was made up of 10 patients who presented with HO Brooker grades 1 and 2 after THA; group 2 comprised 7 patients affected by grades 3 and 4 HO after THA; and group 3 was made up of 18 subjects who presented with one or more preoperative risk factors for developing peri-prosthetic HO before undergoing THA. No positivity for HLA-B27 antigen was observed, but there was as an increase in HLA-B18 (with respect to that in the Sicilian population) in patients with HO following THA. The main conclusion from the study is that there is a strong correlation between the presence of the antigens HLA-A2 and HLA-B18 in patients with HO grades 3 and 4.

Key Words Cementless • HLA system • Heterotopic ossification • Total hip replacement

Introduction

Heterotopic ossification (HO) is a frequent complication of total hip replacement (THR) [1–3] and consists of periarticular new bone formation that probably originates from mesenchymal cells. Non-collagenous proteins (osteonectin, osteocalcin, bone sialoprotein, prostaglandin I (PGI), prostaglandin II (PGII)), and bone morphogenetic protein, a glycoprotein in cortical bone, seem to be involved in HO and may trigger pluripotent mesenchymal cell differentiation [4].

Genetic predisposition may be a cause of HO in individuals where no risk factors can be detected. The prevalence of HO in the second replaced hip in 90% of cases with HO after the first hip arthroplasty seems to support this hypothesis [5, 6]. Analysis of the human leukocyte antigen (HLA) system is used to determine host/donor compatibility in transplantation and HLA analysis may detect subjects at risk of HO formation. To our knowledge, this is the first study on HLA analysis and HO after total hip replacement.

Materials and methods

Thirty-five patients were operated on between January 1997 and January 1999 for cementless THR under regional anesthesia. There were 23 male and 12 female patients. The average age of the patients was 67 years (range, 51–78 years). All the patients were of Sicilian origin. Brooker classification [7] was utilized to detect and

grade HO. The entire series was divided into three groups and all patients underwent histocompatibility typing in order to study first and second class loci. Group 1 was made up of 10 patients who presented with HO Brooker grades 1 and 2 after hip replacement; group 2 comprised 7 patients affected by grades 3 and 4 HO after THR; and group 3 was made up of 18 subjects who presented with one or more preoperative risk factors for developing peri-prosthetic HO before undergoing THR.

HLA system analysis was done on patients in groups 1 and 2 postoperatively while the analysis was conducted pre-operatively for patients in group 3. Typing for antigen HLA I classes A, B, and C was done by the microdroplet lymphocyte toxicity test. HLA II DRB typing was performed by the polymerase chain reaction (PCR) method.

Results

The HLA-A2 antigen was found in 42.8% (15 patients) while the HLA-B18 antigen was observed in 34.2% (12 patients) of the entire study series. The HLA second class DR7 antigen was detected in 17.5% (6 patients). No patient was positive for HLA-B27. More specifically, HLA analysis of group 1 (Table 1) showed 3 patients (30 %) positive for HLA-A2 antigen, 1 patient (10%) for HLA-B18 and 2 patients (20%) for HLA-DR7. Concerning HLA analysis of group 2 (Table 2), the presence of the HLA-A2 antigen was found in 7 patients (100%), of the HLA-B18 antigen in 7 individuals (100%), and of the HLA-DR7 in 2 patients (29%). In Group 3 (Table 3), 5 individuals (28%) were found positive for the HLA-A2 antigen, 4 patients (22%) for the HLA-B18, and 2 (11%) for the HLA-DR7.

Among patients in group 3, two presented radiographic evidence of HO at the 6-month follow-up. One of them presented several risk factors (male, obese, ankylosing spondylitis) prior to surgery and developed grade 3 HO. The other patient had one risk factor (hypertrophic arthritis) and was affected by grade 1 HO. Both subjects presented with HLA-A2 and HLA-B18 positivity. The remaining sixteen patients at the 1-year follow-up did not show any radiographic evidence of HO.

Table 1 HLA analysis of the 10 patients in group 1 (HO Brooker grades 1 and 2). Values are number (%) of positive patients for each subgroup

HLA–A		HLA–B		HLA–C		HLA–DR	
Subgroup	n (%)	Subgroup	n (%)	Subgroup	n (%)	Subgroup	n (%)
A1	3 (30)	B5	2 (20)	C2	1 (10)	DR1	2 (20)
A2	3 (30)	B7	1 (10)	CW7	1 (10)	DR2	1 (10)
A3	2 (20)	B8	1 (10)			DR3	1 (10)
A4	1 (10)	B12	3 (30)			DR4	3 (30)
A9	1 (10)	B13	2 (20)			DR5	2 (20)
A10	2 (20)	B14	1 (10)			DR7	2 (20)
A28	1 (10)	B18	1 (10)			DR9	2 (20)
A69 (28)	1 (10)	B35	1 (10)			DR11	1 (10)
AW19	2 (20)	B44 (12)	1 (10)			DR14	1 (10)
AW36	1 (10)	B51 (5)	2 (20)			DRW 10	1 (10)
AW43	1 (10)	B55	2 (20)			DRW 52	1 (10)
		BW16	2 (20)				
		BW35	1 (10)				

Table 2 HLA analysis of the 7 patients in group 2 (HO Brooker grades 3 and 4). Values n (%) of positive patients

HLA-A		HLA–B		HLA–C		HLA–DR	
Subgroup	n (%)	Subgroup	n (%)	Subgroup	n (%)	Subgroup	n (%)
A2	7 (100)	B8	1 (14)	C3	1 (14)	DR1	1 (14)
A3	2 (29)	B13	1 (14)	C4	1 (14)	DR2	2 (29)
A9	1 (14)	B14	2 (29)	C7	2 (29)	DR3	1 (14)
A10	1 (14)	B18	7 (100)	CW3	1 (14)	DR7	2 (29)
A24 (9)	1 (14)	B21	1 (14)	CW5	1 (14)	DR11	3 (43)
A25 (10)	1 (14)	B44 (12)	1 (14)	CW7	1 (14)	DR13	1 (14)
A69	1 (14)	B51 (5)	1 (14)			DQ3	1 (14)
		BW4	2 (29)			DQ52	1 (14)
		BW6	2 (29)			DRW52	1 (14)

Table 3 HLA analysis of the 18 patients in group 3 (risk factors for HO)

HLA–A		HLA–B		HLA–C		HLA–DR	
Subgroup	n (%)	Subgroup	n (%)	Subgroup	n (%)	Subgroup	n (%)
A1	2 (11)	B5	1 (6)	C3	1 (6)	DR1	1 (6)
A2	5 (28)	B7	2 (11)	C7	2 (11)	DR2	2 (11)
A3	3 (17)	B8	2 (11)	CW3	2 (11)	DR3	2 (11)
A4	2 (11)	B12	1 (6)	CW5	1 (6)	DR4	2 (11)
A9	1 (6)	B18	4 (22)	CW7	1 (6)	DR6	2 (11)
A11	2 (11)	B21	1 (6)	CW8	1 (6)	DR7	2 (11)
A23 (9)	1 (6)	B35	4 (22)			DR8	1 (6)
A24 (9)	2 (11)	B37	2 (11)			DR13	1 (6)
A28	3 (17)	B44 (12)	1 (6)			DR14	3 (17)
		B51	2 (11)			DRW12	2 (11)
		B53	2 (11)				
		BW60 (40)	1 (6)				

Discussion

The HLA system is made up of a series of glycoprotein molecules positioned on the surface of all nucleated cells. The major component of histocompatibility (MHC) is located on the short arm of the sixth chromosome and regulates a large and complex part of the immune system and other aspects of cell proliferation. This particular region contains important genetic traits that seem to greatly influence the susceptibility to various diseases. MHC contains a certain number of loci, specifically the classic HLA antigens (HLA-A, HLA-B, and HLA-C). The MHC region adjacent to the HLA-B locus contains a different set of histocompatibility genes involved in specifying HLA-Ia or HLA-D antigens that control immune responses [8].

At present, the etiology of HO is unknown. However, the identification of some risk factors has led to the use of preventive treatment to limit the onset of HO and has resulted in theories on the pathogenesis HO formation. Systemic and local risk factors of HO have been identified [1–3]. The former include sex (male predominance), old age, obesity, osteoporosis and concomitant diseases, such as hypertrophic arthritis, ankylosing spondylitis, Parkinson's disease, and cranial and spinal cord injuries. Local risk factors are essentially related to surgery and include duration of surgery, muscle mass injury, major blood loss and postoperative hematomas. These local factors may cause inflammation that, in turn, induces bone formation and facilitates differentiation of pluripotent mesenchymal cells into fibroblasts. These then differentiate into chondroblasts and osteoblasts which eventually lead to formation of heterotopic bone tissue.

The possibility of correlating antigen expression and the presence of HO after surgery is most attractive as it would allow us to adopt all of the known preventive measures, to perform minimally invasive surgery and to inform patients on the possibilities of developing HO. Our study revealed a strong correlation between the association of HLA A2 and B18 antigens and the presence of grades 3 and 4 HO.

According to a study conducted by Minaire et al. [9], the percentage of these antigens in Caucasians is as follows: HLA-A2, 49.4%; HLA-B18, 10.7%; HLA-DR7, 22.6%; and HLA-B27, 6.7%. Percentages of first class antigens in the Sicilian population are 41.8% and 8.1% for HLA-A2 and HLA-B18, respectively, 3.9% for HLA-B27 and 23% for HLA-DR7 [10]. The percentage of HLA-A2 locus antigen expression in our study was comparable to that of the Caucasian and Sicilian populations, but it was not statistically significant ($p>0.05$), whereas the expression of HLA-B18 was statistically significant ($p<0.05$).

There is no literature available concerning HO after THR and its relation with the HLA system. However, some reports exist concerning the HLA system and neurogenic para-osteoarthropathies. Minaire et al. [9] studied a population of 43 spinal cord injury and 23 head injury patients and found the presence of HLA-B18 in 25.7% of the 66 patients compared to 7.6% of the controls. Larson et al. [11] examined 21 spinal cord injury patients for HLA-B27 only and reported an incidence of 24% as compared to 0% in the control group. Hunter et al. [12] demonstrated no significant difference in HLA-A and HLA-B antigens in a population of 21 patients with spinal cord injuries and 3 with cerebral injuries complicated with HO. Similar results were reported by Weiss et al. [13] for 12 head injury and 8 spinal cord injury patients.

Garland et al. [8] studied 30 patients with neurogenic non-traumatic HO and found the presence of the HLA-A2 locus in 60% of patients compared to 48.4% in the control

group. Their results did not show a statistically significant increase in the frequency of HLA-B18 and HLA-B27. Seignalet et al. [14] tested 58 French Caucasians with HO after cranial traumatism and found that the association between HLA-B18 and neurogenic paraosteoarthropathies was either weak or absent.

The data presented in our series, concerning an increased presence of HLA-B18, agree with that reported by Minaire et al. [9] but conflict with findings observed by Weiss et al. [13], Hunter et al. [12], Seignalet et al. [14] and Garland et al. [8] concerning the correlation between HO and neurologic diseases. Our study revealed no positivity for the HLA-B27 locus. We assayed second class HLA-DR antigens in the entire study series and observed DR7 positivity in 17.5%.

To our knowledge, this is the first study on HLA analysis and HO after total hip replacement. Our study reveals no positivity for the HLA-B27 locus as well as an increase in HLA-B18 in patients with HO following THR. The main conclusion from the study is that there is a strong correlation between the presence of HLA-A2 and HLA-B18 in patients with grades 3 and 4 HO. The results obtained in our limited study series must be confirmed by future studies on a larger series of patients.

References

1. Mollica Q, Sessa G, Costarella L (1996) Le ossificazioni eterotopiche. G Ital Ortop Traumatol 12(2):1103–1113
2. Nilsson OS (1998) Heterotopic ossification. Acta Orthop Scand 69(2):103–106
3. Nollen JG, Van Douveren FQ (1993) Ectopic ossification in hip arthroplasty. A retrospective study of predisposing factors in 637 cases. Acta Orthop Scand 64:185–187
4. Bosse A, Wuisman P, Jones DB, Schwarz K (1993) Non-collagenous proteins in heterotopic ossification: immunohistochemical analysis in 15 paraplegies. Acta Orthop Scand 64(6):634–638
5. DeLee J, Ferrari A, Charnley J (1976) Ectopic bone formation following low friction arthroplasty of the hip. Clin Orthop 121:53–59
6. Postel M (1974) Les complications des protèses totales de anche. Les ossifications. In: XLIX Reunion Annuelle de la SOFCOT, Paris, pp 83–85
7. Brooker AF, Bowerman MD, Robinson RA, Riley L (1973) Ectopic ossification following total hip replacement. J Bone Joint Surg Am 55(8):1629–1632
8. Garland DE, Alday B, Venos KG (1984) Heterotopic ossification and HLA antigens. Arch Phys Med Rehabil 65(9):531–532
9. Minaire P, Betuel H, Girard R, Pionchery G (1980) Neurologic injuries, para-osteo-arthropathies and human leukocyte antigens. Arch Phys Med Rehabil 61:214–215
10. Illeni MT, Turo G, Veratti MA, Barbanti M, Bombelli G, Bontempelli M (1994) Polimorfismo HLA e popolazione italiana. Trasfusione Sangue 39(1):1–16
11. Larson J, Michalski J, Collacott E, Eltoral D, McCombs C (1981) Increased prevalence of HLA-B27 in patients with ectopic ossification following traumatic spinal cord injury. Rheumatol Rehabil 20:4–8
12. Hunter T, Dubo C, Hildahl CR, Smith NJ, Schroeder ML (1980) Histocompatibility antigens in patients with spinal cord injury or cerebral damage complicated by histocompatibility antigens. Rheumatol Rehabil 19:97–99
13. Weiss S, Grosswasser Z, Orhi A (1979) Histocompatibility antigens in heterotopic ossification associated with neurological injury. J Rheumatol 6(1):88–91
14. Seignalet J, Moulin M, Pelissier J et al (1983) HLA and neurogenic paraosteoarthropathies. Tissue Antigens 21:268–269