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Association of Fatal Aneurysmal Subarachnoid Hemorrhage with Human Leukocyte Antigens in the Finnish Population

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ABSTRACT: Human leukocyte antigens (HLA) have been reported to associate with the risk of aneurysmal subarachnoid hemorrhage (SAH) and poor outcome after SAH. Our aim was to identify HLA antigens that associate with the risk of fatal SAH in the Finnish population.

Medical records of 600 cadaveric organ donors were reviewed to find organ donors that succumbed to SAH ($n = 232$) or brain trauma ($n = 151$). HLA antigen frequencies in these groups were compared with HLA frequenciens in a reference population of 10,000 bone marrow donors. Chi-Square test with Bonferroni correction and multiplicative logistic regression models were used and false positive result probabilities (FPRP) were calculated. Alpha-level was 0.01. HLA-A3 associated with fatal SAH ($p = 0.0014$, OR 1.3 and 95%CI 1.1–1.6) and HLA-DR7 inversely associated with fatal SAH ($p = 0.0040$, OR 0.3 and 95%CI 0.2–0.6). HLA-A3 but not HLA-DR7 showed also a positive trend in donors with brain trauma. FPRP was below 0.5 for HLA-A3, but clearly above 0.5 for HLA-DR7. HLA-A3 seems to associate with fatal SAH in the Finnish population. Further studies are needed to reveal the pathobiologic mechanisms for how HLA-A3 associates with the risk of fatal SAH in Finns. *Human Immunology 68, 100–105 (2007).* © American Society for Histocompatibility and Immunogenetics, 2007. Published by Elsevier Inc.

KEYWORDS: Subarachnoid hemorrhage; aneurysm; inflammation; HLA; brain trauma

ABBREVIATIONS

SCAA	Saccular cerebral artery aneurysm
AAA	Abdominal aortic aneurysm
SAH	Subarachnoid hemorrhage
TBI	Traumatic brain injury
HLA	Human leukocyte antigens
TNF	Tumor necrosis factor

INTRODUCTION

Rupture of a saccular cerebral artery aneurysm (SCAA) causes subarachnoid hemorrhage (SAH), a severe form of hemorrhagic stroke fatal in 40–50% of cases. Aneurysmal SAH affects mainly the otherwise healthy, working aged population [1]. The incidence of SAH is 10–11 per 100,000 in Western countries and twice as high in Finland and Japan [1]. The prevalence of SCAAs in the general population is estimated to be around 2% [2], and approximately 10% of SAH cases have a familial background [3].

The risk of sporadic aneurysmal SAH has been reported to associate with HLA antigens (Table 1). Inflammation of the SCAA wall associates with SCAA rupture [4, 5], and involvement of the immune system and antigen presentation via HLA antigens could be a putative pathobiologic mechanism explaining the observation. Inflammation is involved also in the rupture of

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Received July 23, 2006; accepted November 15, 2006.

0198-8859/07/$–see front matter
doi:10.1016/j.humimm.2006.11.009

TABLE 1 HLA antigens that have been reported to associate with aneurysmal SAH, outcome of SAH, SCAAs, or AAAs as either risk factors or "protective" factors

Author	Population	Number of patients	Linkage associated antigens	Ref.[a]
Reported HLA associations with poor outcome after SAH				
Sakaguchi *et al.*	Japanese	45	Bw60, Aw33, Cw4	[7]
Lye *et al.*	British	40	B7, DR3	[8]
Reported HLA associations of SCAAs				
Sakaguchi *et al.*	Japanese	45	A31, B40	[7]
Norrgard *et al.*	Swedish	45	A28, B40	[18]
Ostergard *et al.*	Danish	116 + 15	B7, DR2	[19]
Ryba *et al.*	Polish	59	Empty DR7	[15]
Mellergard *et al.* (familial SCAAs)	Swedish	15	B7	[20]
Reported HLA associations of AAAs				
Sugimoto *et al.*	Japanese	49	A2, B61	[21]
Rasmussen *et al.*	American	96	DR B1*15, DR B1*04	[22]
Monux *et al.*	Spanish	72	DR B1*01, DR B1*04	[23]
Rasmussen *et al.*	American	142	DR B1*15, DR B1*04	[24]
Hirose *et al.*	Japanese	46	DR2 (15)	[25]
Rasmussen *et al.*	American	37	DR B1*15, DR B1*0404	[26]
Norrgard *et al.*	Swedish	48	No association	[27]

[a] The reported studies have used varying HLA-typing methods during the time period from 1984 to 2003, and may have inconsistencies in the serologic typing methods used. The DR B1*02 allele reported in references 22 and 24 is changed to DR B1*15 according to the novel nomenclature (Tissue Antigens 2005:65;1–55).

abdominal aortic aneurysms (AAA) [6], the risk of which is also HLA-linked, although with different HLA antigens than have been reported to associate with aneurysmal SAH (Table 1).

In addition to the risk of aneurysmal SAH, the risk of poor outcome after SAH has been reported to associate with HLA antigens [7, 8]. A major cause of mortality and morbidity after aneurysmal SAH is the so-called secondary ischemic deficits that develop because of spasm of the cerebral arteries and subsequently impaired cerebral circulation [9]. A major cause of cerebral vasospasm after aneurysmal SAH is inflammation in the subarachnoid space [9, 10]. SAH also causes inflammation [11] and contusion type trauma of the brain parenchyme. Together these findings may explain the association of HLA antigens with outcome after SAH.

Many SCAAs never rupture, but when they do, the consequence is often fatal. To focus invasive therapy, we need diagnostic tools that can identify SCAA carriers at risk of fatal SAH and poor outcome. Prior reports suggest that HLA antigens are linked with risk of aneurysmal SAH and the risk of poor outcome after SAH. Our aim was to identify HLA antigens that associate with the risk of fatal SAH in the Finnish population.

PATIENTS AND METHODS

Medical records of 600 Finnish cadaveric organ donors (years 1998–2004) were obtained from the Donor Registry of the Transplantation and Liver Surgery Unit (H.I.) of the Helsinki University Central Hospital (Helsinki, Finland). HLA data were obtained from the Donor Registry of the Organ Transplantation Unit, and originally determined by the Tissue Typing Laboratory of the Finnish Red Cross Blood Transfusion Service (M.L., I.M.). HLA-A, -B, and -DR typing of the donors were performed serologically (by the complement mediated lymphocytotoxicity on peripheral lymphocytes) and verified by polymerase chain reaction (PCR). The DNA samples were genotyped for HLA-A, HLA-B, and HLA-DRB1 with a commercial kit using the manufacturer's instructions (One Lambda, Inc., Canoga Park, California, USA). A published population of 10,000 HLA-typed bone marrow donors (1–2 per million of the total Finnish population) [12] was used as a reference population. The bone marrow donors were typed with the serologic method, and therefore we used the serologic nomenclature following the standard system determined in International Histocompatibility Workshops.

Statistics

HLA antigen frequencies in the organ donors and in 10,000 Finnish bone marrow donors were calculated and compared with a Chi-Square test using the Bonferroni correction. Alpha-level was 0.01. To evaluate the chance of obtaining a false positive association from the large dataset, a false positive report probability (FPRP) was calculated for the putative association of each HLA antigen and poor outcome after SAH or brain trauma, as described by Wacholder *et al*. [13]. The estimated *a*