Mod Rheumatol (2007) 17:81–82
DOI 10.1007/s10165-006-0541-z

RAPID COMMUNICATION

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HLA-B51 and cigarette smoking as risk factors for chronic progressive neurological manifestations in Behçet's disease

Received: September 13, 2006 / Accepted: October 25, 2006

Key words Behçet's disease · HLA-B51 · Neuro-Behçet's syndrome · Smoking

Central nervous system (CNS) involvement in Behçet's disease (BD) (neuro-Behçet's syndrome; NB) is usually life-threatening, and requires aggressive therapy.[1,2] The most common manifestation of NB includes cranial nerve palsy, dysarthria, pyramidal tract signs, and ataxia with or without consciousness disturbances.[3] Recent studies have disclosed that NB can be classified into acute type and chronic progressive type according to the clinical course.[4] Acute type NB is usually self-limiting, and responds to corticosteroid therapy, although recurrence sometimes takes place. By contrast, the chronic progressive type is characterized by intractable, slowly progressive neurobehavioral changes, ataxia, and dysarthria.[1,4] Of note, patients with the chronic progressive NB show persistent marked elevation of cerebrospinal fluid (CSF) interleukin (IL)-6 despite of the very modest increase in cell numbers and total proteins.[4] Since most patients with the chronic progressive NB presented preceding episodes of the acute type attacks, it is suggested that persistence of some immune reaction within the CNS might play a pivotal role in the development of the chronic progressive neurological damage.[5] Here we explore risk factors for chronic progressive NB.

A total of 150 patients with BD, who visited the clinic or were admitted to the hospital in Teikyo University School of Medicine between 2003 and 2005, were examined for HLA-B51 and habits of cigarette smoking. All 150 patients satisfied the International Study Group criteria for BD[6] (74 men, age 55.6 ± 13.1 years [mean ± SD]; 76 women, age 59.9 ± 14.6 years). We defined chronic progressive NB when the patients satisfied both of the following: the presence of slowly progressive neurobehavioral changes, ataxia, and dysarthria which persist for at least 1 year despite conventional treatment with corticosteroids, cyclophosphamide, azathioprine, and colchicine, and the persistent elevation of CSF IL-6 to more than 20 pg/ml for at least 1 year without any other conditions leading to the elevation of CSF IL-6. Seventeen patients of the 150 had been diagnosed as chronic progressive NB (13 men and 4 women) ($P = 0.0208$). In these 17 patients, HLA-B51 was positive in 16 patients ($P < 0.001$) and habitual cigarette smoking with Brinkman index more than 200 was confirmed in 16 patients ($P < 0.001$) (Table 1). Moreover, 15 of the 17 patients with chronic progressive NB had both HLA-B51 and cigarette smoking habits, compared with 21 of the 133 patients without chronic progressive NB ($P < 0.001$). In male patients, the frequency of HLA-B51, habitual cigarette smoking, or both, was also significantly higher in chronic progressive NB. Ten of the 133 patients without chronic progressive NB had presented self-limiting attacks of acute NB without any progressive CNS manifestations. We next compared the demographic features of these 10 patients with acute NB without progression with those of the 17 patients with chronic progressive NB. As shown in Table 2, the frequency of HLA-B51 or HLA-B51 with habitual cigarette smoking but not that of habitual cigarette smoking alone was significantly higher in chronic progressive NB than in acute NB, whereas there were no significant differences in sex between these two groups. These results indicate that HLA-B51 and cigarette smoking, and especially their combination, are risk factors for chronic progressive NB.

Previous studies have confirmed the role of the *HLA-B*51* gene in the pathogenesis of BD, although the contribution to the overall genetic susceptibility to BD was estimated to be only 19%.[7] Our data further suggest that the *HLA-B*51* gene in combination with cigarette smoking might play a pivotal role in the persistent progression of CNS inflammation in BD. Because there was no significant correlation of Brinkman index with chronic progressive NB (data not shown), it is unlikely that the progression of the CNS inflammation might result from direct accumulating toxicity of cigarettes. Of note, recent studies have demon-

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Table 1. Demographic feature of Behçet's disease patients with or without chronic progressive neuro-Behçet's syndrome (NB)

	Chronic progressive NB		*P* value[a]
	No (n = 133)	Yes (n = 17)	
Sex (male/female)	61/72	13/4	0.0208
Cigarette smoking (+/–)	56/77	16/1	<0.0001
HLA-B51 (+/–)	53/80	16/1	<0.0001
HLA-B51 and smoking (+/–)	21/112	15/2	<0.0001
Male/smoking (+/–)	38/23	12/1	0.0494
Male/HLA-B51 (+/–)	25/36	13/0	<0.0001
Male/ HLA-B51 and smoking (+/–)	16/45	12/1	<0.0001

[a] Evaluated by Fisher exact test

Table 2. Demographic feature of Behçet's disease patients with acute neuro-Behçet's syndrome (NB) or chronic progressive NB

	Acute NB (n = 10)	Chronic progressive NB (n = 17)	*P* value[a]
Sex (male/female)	6/4	13/4	0.4147
Cigarette smoking (+/–)	8/2	16/1	0.5350
HLA-B51 (+/–)	4/6	16/1	0.0042
HLA-B51 and smoking (+/–)	3/7	15/2	0.0036
Male/smoking (+/–)	6/0	12/1	1.000
Male/HLA-B51 (+/–)	2/4	13/0	0.0039
Male/HLA-B51 and smoking (+/–)	2/4	12/1	0.0173

[a] Evaluated by Fisher exact test

strated that HLA-DR4 in combination with cigarette smoking is a risk factor for the expression of anti-cyclic citrullinated peptide antibody and thus for the progression of rheumatoid arthritis.[8] Certain substances in cigarettes might play a role as an antigen that is presented in the context of HLA-DR4 to T cells.[8] Similarly, it is likely that certain substances in cigarettes might be immunogenic in the presence of HLA-B51, resulting in the persistent activation of immune responses within the CNS in BD. Further studies to identify such substances that can be presented in the context of HLA-B51 to T cells is important for the delineation of the mechanism of NB.

References

1. Hirohata S, Kikuchi H. Behçet's disease. Arthritis Res Ther 2003;5:139–46.
2. Serdaroglu P. Behçet's disease and the nervous system. J Neurol 1998;245:197–205.
3. Siva A, Altintas A, Saip S. Behçet's syndrome and the nervous system. Curr Opin Neurol 2004;17:347–57.
4. Hirohata S, Isshi K, Oguchi H, Ohse T, Haraoka H, Takeuchi A, et al. Cerebrospinal fluid interleukin-6 in progressive Neuro-Behçet's syndrome. Clin Immunol Immunopathol 1997;82:12–7.
5. Hirohata S. Histopathology of central nervous system lesions of Behçet's Disease. Clin Exp Rheumatol 2004;22(Suppl 34):S-131.
6. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet 1990;335:1078–80.
7. Gül A, Hajeer AH, Worthington J, Barrett JH, Ollier WE, Silman AJ. Evidence for linkage of the HLA-B locus in Behçet's disease, obtained using the transmission disequilibrium test. Arthritis Rheum 2001;44:239–40.
8. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54:38–46.