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Review Article

Influence of Human Leukocyte Antigen in Susceptibility to Migraine in Patients

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Abstract: Migraine affects more than one billion individuals each year across the world, and is one of the most common neurologic disorders, with a high prevalence and morbidity, especially among young adults and females. Migraine is associated with a wide range of comorbidities, which range from stress and sleep disturbances to suicide. The complex and largely unclear mechanisms of migraine development have resulted in the proposal of various social and biological risk factors, such as hormonal imbalances, genetic and epigenetic influences, as well as cardiovascular, neurological, and autoimmune diseases. Experimental findings suggest an involvement of neuroinflammatory mechanisms in the pathophysiology of migraine. Specifically, preclinical models of migraine have emphasized the role of neuroinflammation following the activation of the trigeminal pathway at several peripheral and central sites including dural vessels, the trigeminal ganglion, and the trigeminal nucleus caudalis. The evidence of an induction of inflammatory events in migraine pathophysiological mechanisms has prompted researchers to investigate the human leukocyte antigen (HLA) phenotypes as well as cytokine genetic polymorphisms in order to verify their potential relationship with migraine risk and severity. Furthermore, the role of neuroinflammation in migraine seems to be supported by evidence of an increase in pro-inflammatory cytokines, both ictally and interictally, together with the prevalence of Th1 lymphocytes and a reduction in regulatory lymphocyte subsets in peripheral blood of migraineurs. Cytokine profiles of cluster headache (CH) patients and those of tension-type headache patients further suggest an immunological dysregulation in the pathophysiology of these primary headaches, although evidence is weaker than for migraine.

Keywords: HLA, Migraine, Disease, Antigen.

INTRODUCTION

Migraine is a common neurological disorder of which severe, recurrent headaches may be a predominant symptom [1]. Typically, the associated headache affects one side of the head, is pulsating in nature, may be moderate to severe in intensity, and could last from a few hours to three days [1]. Non-headache symptoms may include nausea, vomiting, and sensitivity to light, sound, or smell [2]. The pain is generally made worse by physical activity during an attack [3], although regular physical exercise may prevent future attacks [4]. Up to one-third of people affected have aura: typically, it is a short period of visual disturbance that signals that the headache will soon occur [5]. Occasionally, aura can occur with little or no headache following, but not everyone has this symptom [6].

Migraine is believed to be due to a mixture of environmental and genetic factors [7]. About two-thirds of cases run in families [5]. Changing hormone levels may also play a role, as migraine affects slightly more boys than girls before puberty and two to three times more women than men [8]. The risk of migraine usually decreases during pregnancy and after menopause [8]. The underlying mechanisms are not fully known. They are, however, believed to involve the nerves and blood vessels of the brain [5].

Family and twin studies, derived from the observation of familial cases, provided conflicting results regarding the mode of inheritance [9, 10]. In a large proband-oriented clinical study, first-degree family members of probands with

migraine without aura had increased relative risk ratios, compared to the general population, for both migraine with aura ($\lambda = 1.4$) and migraine without aura ($\lambda = 1.9$). First degree family members of probands with migraine with aura had a nearly four-fold increased risk ratio ($\lambda = 3.8$) for migraine with aura, but not for migraine without aura [11]. This suggests that genetic factors are involved in both types of migraine, but are strongest in migraine with aura. The relative risk ratio for a sibling (λs), defined as the ratio of the prevalence of a disease in siblings of affected individuals divided by the prevalence of a disease in the population, can be calculated [12]. The first studies on HLA antigens in migraine were performed by Kudrow in 1978 [13] and O'Neill et al. in 1979 [14]. In a 1987 study of eight households, the distribution of migraine haplotypes shared by sib-pairs was greater than expected; it was hypothesized that migraine heredity was HLA linked [15]. To explain an association between HLA and non-immunologic disease, such as migraine, it has been hypothesized that HLA antigens interfere with the interaction between receptors and ligands on cell membranes [16]. Regarding the biological function of the HLA antigens, the observed decreased frequency of the DR2 antigen in migraine with aura patients suggests that the presence of DR2 means resistance to the disease. Because a relative risk lower than 1 is considered a sign of protection against disease, DR2 antigen or another gene of resistance in linkage disequilibrium with DR2 may be assumed to control the disease, the receptor expression at cellular level, or both [17]. The demonstration of a clear genomic difference between migraine with and without aura may provide an additional basis for the proposed difference within these two clinical entities [18], and it may represent another step in decifering the genetic basis of migraine [19]. To identify genes in the HLA region that are involved in migraine heredity, it will be useful to study polymorphisms of other genes located in the region.

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