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Platelet Alloantigen Polymorphism and Migraine Headache - An Observation in the Malaysian Population at Kelantan

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Introduction

Migraine is a common disabling disorder characterized by recurrent headaches and at times non-painful episodic phenomena associated with a variety of neurological manifestations. It ranks among the top 20 causes of disability worldwide [1]. It therefore has a substantial impact on individuals as well as on society. A community based study on headaches in Malaysia showed the prevalence of migraine to be 9% in the population [2]. Evidence to support that genetic factors are involved in migraine, especially in migraine with aura has accumulated during the past few years [3]. First-degree relatives of probands who have migraine with aura have a four-fold increased risk of migraine (with aura).

Serotonin, Platelets and Migraine

Extracranial arterial dilation during an attack was assumed to be the main cause for the migraine pain, because it was observed that vasoconstrictors such as sumatriptan alleviated migraine pain [4]. Diminished levels of central serotonin associated with an increase in serotonin release during migraine attacks confirm that serotonin metabolism is implicated in the pathogenesis of migraine [5]. The observation that fluctuations in the serotonin levels in the median raphe nuclei of the brain, which is reflected in the platelet levels of serotonin before, during and after the migraine attacks is convincing enough to incriminate serotonin in the pathogenesis of migraine. Sakai et al. [6] reported that serotonin synthesis in the brain was highest during the migraine attacks, lowest after sumatriptan and intermediate when patients were migraine free. Whether peripheral circulating serotonin in the blood can influence a migraine attack is not clear since serotonin per se does not penetrate the human blood brain barrier. However animal experiments have proved that serotonin can penetrate the blood brain barrier leading to changes in the electrical activity of the cortex [7]. It is of interest however to note that as early as in 1976 it was observed that the platelets from classical migraine patients showed a higher tendency for spontaneous aggregation and adhesion during the headache-free period when compared with the platelets from controls [8]. Similarly, serotonin release from the platelets within three days of a migraine attack was found to be significantly less than that measured during a migraine-free interval [9]. Though serotonin is still considered to be a key molecule in the neurobiology of migraine, the exact role of brain serotonergic mechanisms still remains a matter of controversy [10].

The first platelet receptor to be scrutinized was the integrin αIIbβ3 (designated as glycoprotein IIb/IIIa), the most abundant receptor on the platelet membrane surface. This mediates platelet aggregation via the binding of adhesive proteins, such as fibrinogen and von Willebrand factor (vWF) [11]. The genes encoding glycoprotein IIb and IIIa are located on chromosome 17q21.

Amino acid substitutions in platelet membrane glycoprotein result in alloantigens. As a result human platelet alloantigen HPA-1a or PlA1 molecules have a leucine, whereas HPA-1b or PlA2 proteins have a proline in their configuration [12]. These inherited polymorphisms within the platelet membrane glycoprotein genes can alter their antigenicity, regulate their expression levels and modulate their functional properties. Possession of an A2 allele or the polymorphic state (A1/A2) increases the tendency for platelet hyper-aggregation and thus can also act as a trigger for initiating a migraine attack as mentioned earlier.

Our study was to reckon the pattern of occurrence of the A1/A2 allele on the platelet membrane in normal controls as well as in the platelets of migraine patients. Allele frequencies and polymorphisms of the PlA1/ PlA2 of the glycoprotein IIIa gene among the population in Malaysia had been published elsewhere by us earlier [13].

Methodology

80 patients diagnosed as having migraine headaches and 80 age-matched controls (a total of 160 individuals) underwent molecular study to investigate the platelet alloantigen configuration in the glycoprotein IIIa gene on the platelet surface. Their genotype configuration (PlA1/ PlA2) was determined using allele-specific PCR amplification technology, employing the allele specific oligonucleotide (ASO) technique.

Of the 80 patients, 24 patients had aura (30%), 47 patients were unable to attend to their routine work due to the headache (58.7%), 57 patients had severe intensity of headache (71.2%), 62 patients had nausea and or vomiting (77.5%) and 53 patients had photophobia or phonophobia (66.2%) (Table 1).

Characteristics	Number of patients (n=80)	(%)
Aura		
Yes	24	30.0
No	56	70.0
Disability to work		
Yes	47	58.7
No	33	41.3
Intensity (Severe headaches)		
Yes	57	71.2
No	23	28.8
Nausea/Vomiting		
Yes	62	77.5
No	18	22.5
Photophobia/Phonophobia		
Yes	53	66.2
No	27	33.8

Table 1: Clinical characteristics of migraine cases (n=80).

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Variables	Migraine with A2 allele n=4	Migraine without A2 allele n=76	OR (95% CI)	p-value*
Aura				
Yes	3	21		
No	1	55	0.77-79.81	0.08
Disability				
Yes	3	44		
No	1	32	0.21-21.94	0.5
Intensity				
Yes	3	54		
No	1	22	0.12-12.39	0.8
Nausea/Vomiting				
Yes	4	58		
No	0	18	NA	NA
Photophobia/ Phonophobia				
Yes	2	51		
No	2	25	0.06-3.68	0.4

NA: Not Applicable; *: Simple logistic regression

Table 2: Distribution of clinical manifestations in migraine patients with or without the A2 allele.

Results

The overall frequency of PlA1/A1 and PlA1/A2 alleles in this study (n=160) is shown in the Table 2. The frequency PlA1/A1 genotype (homozygous) in both the patients and controls included in this study was 95.6% and that of PlA1/A2 genotype (polymorphism) was 4.4%.

The frequency of the PlA1/PlA1 (homozygous) genotype in patients with migraine was 95.0% as compared with 96.2% in controls, and the PlA1/PlA2 (heterozygous) frequency was 5.0% in patients as compared with 3.8 in controls. The difference is therefore not statistically significant (P >0.05). Thus there was no difference in the genotype distribution between the migraine cases (taken as a whole) and controls (Table 2).

However, a pertinent observation was made in that 75.0% or majority of cases with the PlA1/PlA2 polymorphism (3 out of the 4) had aura, disability, vomiting and severe headaches when compared with the migraine group without the PlA2 allele. Since, the sample size (with the PlA2 allele) is quite small, the p value cannot be considered significant (Table 2).

Conclusion

Detailed study of the molecular structure of GPIIb/IIIa on the platelet surface has thrown light on the importance of the PlA alleles in the genes of human beings. The homozygous state of PlA1/PlA1 allele configuration in the GPIIIa structure in the human platelets is much more common than the heterozygous state of PlA1/PlA2 allele configuration. It has been shown that the PlA1/PlA2 polymorphic state increases the risk of platelet adhesivity and serotonin release. A disorder like migraine, which apparently appears unrelated to coronary thrombosis, still shares a common mechanism wherein platelet adhesion is a common and an important underlying factor in both the disease conditions. Serotonin release has been incriminated in the mechanism production of headache in migraine. Classical migraine, having a four-fold increased risk of inheritance gives further support to the finding that PlA alloantigens (which are inherited) could play a vital role in the genesis of migraine [3].

From our study (though small in number) it appears that severe headaches, nausea/vomiting and aura are likely to be seen more commonly in the migraine patients with the PlA2 polymorphism.

Summary

This was a study to identify the presence of the allelic configuration on the glycoprotein IIb/IIIa (GPIIIa) of the platelet membrane in patients with migraine and in controls, with special reference to the presence of the homozygous state PlA1/PlA1 or the heterozygous state PlA1/PlA2 (PlA refers to the platelet alloantigen and the A1 and A2 refers to differing amino acid patterns on the concerned allele).

80 cases of migraine and 80 age matched controls were studied on a prospective basis. It was found that 76 of the 80 cases with migraine possessed the PlA1/PlA1 configuration (homozygous) while merely 4 migraine cases possessed the PlA1/PlA2 configuration (polymorphic or heterozygous). The controls had a more or less similar proportion of homozygous and polymorphic configuration (i.e., 77 were PlA1/PlA1 positive and 3 were PlA1/PlA2 positive).

The individual symptoms were reviewed in the light of the allele status but they did not differ substantially from group to group. But one parameter deserves mention as a striking observation. It was found that the majority of cases (though the number remains small) with PlA1/PlA2 polymorphic state had classical migraine with aura, intense headaches and vomiting as part of their migraine headaches. The exact pathophysiology or relationship of this classical migraine to the PlA1/PlA2 polymorphic state remains unclear.

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