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A Mini Review on Migraine and Hypercoagulability

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ABSTRACT

The relationship between migraine and hypercoagulability and also the relationship between migraine with aura and the risk of arterial ischemic stroke in children has not been well established. The results of the studies about hypercoagulability in childhood migraine are very few and conflicting. There are lots of questions to be answered that necessitates for multi-centre studies on large populations.

Keywords: Childhood, Migraine, Stroke and hypercoagulability

MIGRAINE AND HYPERCOAGULABILITY

Migraine is one of the most common neurologic conditions in pediatrics characterized by episodic headaches of moderate to severe intensity. A recent meta-analysis of 64 cross-sectional epidemiological studies of pediatric and adolescent migraine including 227,249 subjects from 32 countries yielded an estimated overall mean prevalence of 9.1% [1]. In contrast, childhood arterial ischemic stroke (AIS) is an uncommon occurrence, with an estimated incidence of 1.6 per 100000 children per year in a recent population-based study [2].

In adults, especially in premenopousal women migraine with aura (MA) is considered to be a risk factor for stroke [3,4]. However, the relationship between migraine with aura and risk of cerebral infarct in children has not been well established. Children with AIS are younger than those with migraine. Migraine with aura is less common in children under 8 years of age, with a prevalence of 3% to 4% in children aged 3 to 7 years, versus 23% to 31% of teenagers [5]. By comparison, previous research suggests that approximately half of childhood AIS occurs in children aged less than 5 years at symptom onset [2]. This controversy makes more difficult to understand the relationship between stroke and migraine with aura in childhood.

Shared genetic mutations and inflammation, vascular reactivity, endothelial dysfunction, electrical/depolarizing and hypercoagulable states have been suggested as putative mechanisms for both migraine and stroke. Migraineurs were found to have higher levels of platelet aggregation, von Willebrand factor and higher prevalence of hypercoagulable states [4,6,7].

One of the most interesting hypotheses is the occurrence of prothrombotic conditions, which may lead to cerebral ischemia during migraine attacks [7]. Peatfield advanced his hypothesis that micro-emboli following platelet aggregation could cause either aura or transient ischemic attack (TIA) [8]. Another potential mechanism linking migraine with aura and hypercoagulability is that cortical spreading depression (CSD) leads to weakening of the blood brain barrier and endothelial damage, as well as eliciting the inflammatory cascade in neurons and glial cells with subsequent activation of peripheral and central trigeminovascular neurons. These CSD-related changes promote a thrombophilic environment [9]. Migraine, especially with aura, is associated with high estrogen states, thrombocytosis, erythrocytosis, and elevated circulating levels of vWF antigen, fibrinogen, tPA antigen, and endothelial microparticles. Studies evaluating the relationship of migraine to aPL, homocysteine, Protein S and the MTHFR C677T polymorphism show conflicting results, Meta-analyses about adult migraine patients refute a link between migraine, Factor V Leiden and the prothrombin gene mutation [9].

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In children, there are few papers about the association between thrombophilia and migraine and the results are controversial. Pilarska et al. [10] showed increased aPL, but another study failed to prove significant increase in aPL levels [11]. Kutai et al. [12] reported aPL was found in 6 of their 44 patients with migraine and LA was demonstrated in 11. According to the results of Avcin et al, the prevalence of aCL does not appear to be increased in an unselected group of children with migraine [13]. Ferrara et al. [6] showed that, in children with migraine, aPL does not differ significantly from controls.

Genetic factors related to thrombophilia were studied and the results were controversial. F5 A1691G was more common in patients with migraine with aura and ischemic stroke compared to the control group [14]. Other studies failed to demonstrate F5 A1691G or other risk factor(s) for hypercoagulability in patients suffering from migraine [15]. Kutai et al. [12] found that, F5 A1691G and F2 G20210A were significantly more frequent among children of Jewish origin, compared to the control group of the same ethnic origin and also significantly increased factor VIII activity in 25% of the migraine patients. Ferrara et al. [6] found significantly increased prevalence of factor V Leiden (FVL) and MTHFR677T in migraine patients when compared with controls but without significant differences for the F2 polymorphism and also increased FVIII and FIX activities. Herak et al. [16], investigated the prevalence and possible association of inherited prothrombotic risk factors in children with stroke, transient ischemic attack or migraine and revealed the presence of the human platelet alloantigen-2b allele was associated with a 2.23-fold increased risk for migraine, but factor V G1691A and factor II G20210A were not associated with an increased risk for migraine in children in their study. Bottini et al. [17] found a trend toward an increased risk of migraine in subjects carrying a homozygous mutant genotype for MTHFR C677T and MTHFR A1298C polymorphisms and also Herak et al. [16] found an increased risk for migraine in children homozygous for MTHFR C677T although the association was not statistically significant but different results obtained by Bassi et al. [18]. We reported higher Lp(a) concentrations in our migraine patients according to the healthy controls, that can be a sign of a vascular event risk [19].

In the literature there are few case report series including 1or 2 patients with migrainous infarct in children. None of them have reported the relationship of migrainous stroke with a thrombophilic risk factor [20-25]. Riikonen and Santavuori [26] reported that migrainous stroke was diagnosed in six of 42 children suffering from arterial stroke. No physiologic anticoagulant deficiency or anti-phospholipid syndrome was found. Two patients had mitochondrial disease (MELAS).

There are lots of question about childhood migraine and hypercoagulability and also the relationship between childhood migraine and stroke. Does really hypercoagulability induces migraine attacks with aura by a microemboli or the hypercoagulability is the result of a migraine attack via inflammation, vascular reactivity, endothelial dysfunction. Does migraine really causes stroke or the two entities shares the same vascular risk factors like ıncreased levels of c-reactive protein, ıncreased body weight, high blood pressure, hypercholesterolemia, ımpaired insulin sensitivity, high homocysteine levels. The presence of genetic mutations associated with thrombophilia may be an additional risk factor in patients with migraine who subsequently could develop AIS. Another question is: Is it really necessary to search for thrombophilia in all patients with MA or limit the searching for patients only with elongated aura, hyperlipidaemia, valvular heart disease, patent foramen ovale, arterial hypertension, parental history of stroke or deep vein thrombosis, white matter abnormalies on brain magnetic resonance imaging.

For answering all of these questions, there is need for multi-centre studies about endothelial dysfunction, vascular flow velocity, inflammation markers, platelets and acute phase reactants both during migraine attacks and between attacks on large populations to confirm these correlations in childhood.

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