

## Editorial

# Migraine and Cerebral Infarction

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Many studies show an association between migraine and cerebral infarction [1-4]. The association may be stronger among young subjects and especially when it comes to migraine with aura [5]. However, this topic is controversial [6]. Several mechanisms have been proposed to explain this possible association. 1. The association is spurious. 2. Migraine and cerebral infarction have shared risk factors. 3. Migraine may sometimes cause cerebral infarction. 4. Cerebral infarction may cause migraine's attacks (symptomatic migraine). This article will discuss the different possible causes for the association between migraine and cerebral infarction and clinical implications.

## Spurious association

Some patients with migraine suffer from persistent aura [7]. This is well documented in familial hemiplegic migraine [8]. In some cases it is possible that persistent aura may be misdiagnosed as cerebral infarction. Because cerebral infarction is rare among young adults and migraine frequent, it is possible that this misdiagnosis may account for at least part of the association between migraine with aura and cerebral infarction in young adults. This spurious association may explain that especially migraine with aura is associated with cerebral infarction. Novel studies based on DWI should reduce or eliminate this error.

## Shared risk factors

Higher frequencies of smoking, elevated blood pressure and parental history of early myocardial infarction have been reported among migraineurs compared to controls [9]. Progression of migraine is associated with obesity, stressful life events, and snoring [6]. These are risk factors also reported to be associated with cerebral infarction. Shared cerebrovascular risk factors may therefore account for part of the association between migraine and cerebral infarction.

## Migraine causes cerebral infarction

The association between migraine and cerebral infarction pertains especially to migraine with aura [1]. It is thought that migraine with aura is caused by cortical spreading depression which is a depolarizing wave inducing reduced cell functioning. It has been speculated that cortical spreading depression may induce ischemia and infarction in susceptible patients. This may explain the association between cerebral infarction and migraine with aura (as opposed to migraine without aura).

Electrophysiological evidence indicates spreading depolarization's in acute cerebral infarction. These depolarizations resemble cortical

spreading depression and may promote cell death in ischemic brain tissue [10]. The International Headache Society has established criteria for diagnosing migrainous cerebral infarction [11]. Other mechanisms include activation of platelets and it has been suggested that this may cause cerebral infarction [12].

Whether cortical spreading depression may cause infarction in normal brain tissue is controversial. Clinical experience suggests that cortical spreading depression does not respect arterial territories. To my knowledge, there is little evidence of possible migrainous cerebral infarction not restricted to arterial territories. It is likely that migraine induced cerebral infarction contributes little if at all to the association between migraine and cerebral infarction [12].

## Cerebral infarction causes migraine aura

As reported above, electrophysiological studies suggest that cerebral infarction may cause peri-infarct de polarizations. It is also a frequent clinical experience that some patients with cerebral infarction and corresponding DWI lesions on MRI report typical migraine aura symptoms. A likely explanation is that acute cerebral infarction induces migraine aura with or without headache in susceptible patients [12]. In some patients with cerebral infarction, the migraine aura symptoms dominate the clinical presentation and some patients have aura symptoms without simultaneous neurological deficits. Thus it is possible that some patients with migraine suffer from more severe symptoms in the early phase of cerebral infarction than patients without migraine. It is therefore conceivable that migraineurs with acute cerebral infarction are more prone to seek medical help because of more severe symptoms than patients without migraine. In support of this, we recently published a study showing that migraineurs had significantly more embolic strokes (versus lacunar strokes) than non-migraineurs. In addition, cortical infarctions were significantly smaller among migraineurs compared to non-migraineurs [13]. The findings were independent of age. Thus, small cortical infarctions seem to be more often symptomatic in migraineurs than among non-migraineurs and this may explain at least part of the association between migraine and cerebral infarction.

That cerebral infarction may cause migraine aura (symptomatic migraine) has implications for stroke treatment. Thrombolysis needs to be administered within 4.5 hours of stroke onset and it is sometimes difficult to differentiate between acute cerebral infarction and migraine aura. Thus we found that migraine was associated with low rate of thrombolysis in patients with acute cerebral infarction in our department [14]. On the other hand, thrombolysis is often given to stroke mimics including migraine. Fortunately, thrombolysis in stroke mimics seems to be safe [15].

## Comments

There are several possible mechanisms underlying the association between migraine and cerebral infarction. In my opinion, the most dubious is that migraine aura causes cerebral infarction, not least because migraine aura is very common [16]. Even among patients

with cerebral infarction that agree with the International Headache Society criteria of migraine stroke, it is more probable that the cerebral infarction caused migraine aura than vice versa.

That cerebral infarction may cause migraine aura symptoms and thereby account for perhaps most of the association between migraine and cerebral infarction, has important clinical implications. It is well-known that cerebral infarction is associated with oral contraceptive drugs (OCD), and patent foramen ovale (PFO). Both OCD and PFO are associated with migraine. If migraineurs with small cortical infarction are more prone to seek medical help than non-migraineurs, this may explain at least part of the association between OCD and PFO and cerebral infarction. That cerebral infarctions among patients with PFO tend to be small supports this possibility [17]. Thus, there may be no direct causal mechanisms between OCD and PFO.

In my opinion, migraineurs should be reassured that the risk of cerebral infarction is not much different from non-migraineurs.

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