Migraine as a Risk Factor for Subclinical Brain Lesions (CAMERA-1 studies of brain lesions in migraine)

JAMA, 2004 Jan 28; 291 (4): 427-434

Migraine was considered an independent risk factor for stroke, yet at the time of this article, the evidence for this association was restricted to a select subpopulation of women with migraine, and data on the prevalence of associated subclinical infarcts was lacking in patients with migraine. Nonetheless, prior clinic-based MRI studies from patients with migraine had suggested an increased risk for subclinical white matter lesions (WMLs), though many of these studies did not account for concurrent cardiovascular risk factors or vasoconstrictor use (i.e., triptan) as potential contributing factors to these WMLs as well. As such, using a large population-based MRI design, the goal of this study was to quantify and qualify the relationship between migraine and subclinical brain infarcts or WMLs, in a more generalized migraine population.

Experimental Design and Statistics:

This was a cross-sectional study (i.e., observational study; one point in time) using cases and controls selected from the Genetic Epidemiology of Migraine study, specifically males and females aged 20-60 years old from 2 Dutch municipalities. Patients with migraine (with and without aura) were identified based on initial screening data and a headache questionnaire from the International Headache Society. Of the patients selected, 134 patients with migraine without aura and 161 patients with migraine with aura participated in the full study. A set of 140 age, sex, and municipality-matched controls were selected as well, yielding 3 patient groups for statistical comparison. All selected patients underwent an initial telephone interview followed by an in-person clinic visit for a brain MRI (1.5T unit), blood work, and a neurological exam. MRIs were analyzed by a blinded Neuroradiologist, and both infarcts and WMLs were defined based on strict imaging criteria. If several infarcts were identified, each was scored based on their location and vascular supply. WMLs were characterized as periventricular (PVWML) or deep (DWML) and were numerically scored to obtain a final score or "load" based on size, location, and number. Statistically, all patient characteristics were compared using Chi Square analyses, t-tests or one-way ANOVAs. Logistic regression models were used to quantify the risk (ORs) of prior brain infarcts or WMLs (PVWML or DWML) based on migraine status, subtype, and attack frequency. Select patient characteristics or sociodemographic data were included into regression models as well.

Results:

Baseline sociodemographic and medical characteristics/comorbidities were quite similar in the 3 patient groups (Table 1). Regarding imaging data, patients with migraine were more likely to have subclinical brain infarcts (60 total infarcts, 8%) vs. non-migraine patients (9 total infarcts, 5% of population, Tables 2 & 3). Although some infarcts were lacunar or of the anterior circulation, most (57% of infarcts) were within the posterior circulation territory (PCT), specifically the cerebellum. Further, most of these PCT infarcts were found in migraine patients with aura (13 vs. 3 in migraine without aura patients) and the risk for PCT infarcts increased with a higher monthly attack frequency in migraine patients with aura (OR of 15.8 in this subgroup). Otherwise, PCT infarct risk was slightly lowered by prior ergotamine use, but it was unchanged by prior triptan use. In addition to PCT infarcts, women (but not men) with migraine (both subtypes) were also at a greater risk for a high DWML load. Specifically, the OR for a high DWML load was 2.1 in women with migraine, and, again, the risk increased with a higher monthly attack frequency. Otherwise, the risk for high DWML load was only slightly increased by a prior history of HTN, tobacco use, or prior ergotamine use (in those with $\geq$1 attack per month), but the risk was not affected

by prior triptan use (Table 4). Finally, there were no differences in the size or number of PVWMLs in the migraine vs. control populations.

Conclusions:

This was a comprehensive, MRI-based study in a generalized migraine population that identified a higher risk for PCT infarcts and DWMLs in patients with migraine, covarying for other cardiovascular and medication-related variables. The etiology for PCT infarcts in patients with migraine is unclear, but the study authors speculated that vasculopathies, small embolic events, or generalized vessel narrowing, rather than atherosclerotic disease, were more likely to contribute. Further, regarding mechanisms for both PCT infarcts and DWMLs, hemodynamic variables and local changes induced by migraine (reduced perfusion pressure, clotting system activation, vasoconstriction, cytokine release) may both precipitate and/or enhance the risk for thrombus formation. Of note, higher monthly attack frequency enhanced both PCT infarct and DWML risk in migraine patients, suggesting that our efforts at controlling migraine frequency in the clinical setting is of utmost importance. Overall, this study certainly prompted further assessments into the etiologies for these lesions in migraine, and several follow up and longitudinal studies have since been completed.

Associated reading, if interested:

1) **Infarcts in the posterior circulation territory in migraine: the population-based MRI CAMERA study** (Brain, 2005 Jul 8; 128: 2068-2077).
2) **Brainstem and cerebellar hyperintense lesions in migraine** (Stroke, 2006 Feb 23; 7(4):1109–1112).
3) **Structural brain changes in migraine** (JAMA, 2012 Nov 14; 308(18): 1889 – 1897).

Summary completed by Elaine Sinclair, DO/PhD