Stroke Risk Is Increased In Migraine With Aura

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SAN FRANCISCO — Women who have migraine with aura could be at increased risk for ischemic stroke, Leah MacClellan said at the 32nd International Stroke Conference.

She reported findings from a population-based case-control study of 386 women aged 15-49 years who presented with a first, nontraumatic ischemic stroke and 614 controls matched for age, race, and region.

The investigators stratified the odds of stroke among women with a history of migraine with aura, compared with women who did not have a history of migraine, by the presence of hypertension, diabetes, or myocardial infarction.

Women with migraine onset in the past year, compared with women with no history of migraine, had a significant 6.7-fold increased risk of stroke.

The associations were strongest among those with no history of these classic stroke risk factors, Ms. MacClellan explained at the conference, which was sponsored by the American Stroke Association.

For example, the odds ratio for stroke in those with migraine plus aura versus those with no history of migraine was 0.8 in those with hypertension, compared with 1.7 for those without hypertension; 1.2 in those with diabetes, compared with 1.5 in those without diabetes; and 0.2 in those with a history of MI, compared with 1.6 in those with no history of MI, said Ms. MacClellan of the University of Maryland, Baltimore. All associations were statistically significant.

"This finding is important because it suggests migraine might contribute to stroke independent of these classic risk factors," she said.

A similar analysis stratifying stroke risk based on current smoking and oral contraceptive use in women with migraine plus aura, compared with women with no history of migraine, showed the associations between migraine with aura and stroke were the same regardless of smoking or OC use. However, the interaction between smoking and OC use was shown to be important, she reported.

Compared with women with migraine plus aura alone, those who smoked and had migraine plus aura had a significant 2.3-fold increased risk of stroke, as did those with migraine plus aura who used oral contraceptives. Women with migraine plus aura who smoked and also used OCs had a significant 7.3-fold increase in the odds of stroke.

"This finding is important because these are modifiable risk factors," Ms. MacClellan noted.

Another finding of note from this study was that onset of migraine with aura in the past year was associated with increased stroke risk. Those with onset in the past year, compared with those with no history of migraine, had a significant 6.7-fold increased risk of stroke.

Those with a migraine history of more than 12 years had a non–statistically significant 1.4-fold increase in stroke risk. This finding contrasts with those from at least one other study showing that long-term migraine history was associated with increased stroke risk, she said.

The possibility that unrecognized disorders might explain the association between recent migraine onset and stroke risk in the current study warrants additional study, she said during a discussion that followed her presentation.

There was no evidence in the current study of a role for patent foramen ovale in mediating the association between migraine with aura and stroke, nor was there any evidence for preferential infarct location in terms of anterior and posterior circulation in those patients with migraine plus aura.

Patients in this study were identified from discharge data from 59 hospitals, and all had stroke that was confirmed by CT or MRI. Controls were ascertained by random digit dialing.

Migraine with aura was defined as headache with aura at least twice per year, with spots, lines, flashing lights, or loss of vision occurring around the time of the headache. Migraine without aura was defined as at least five headaches per year with nausea, vomiting, or sensitivity to light during headache, and no history of visual aura.

Migraine with aura was reported by 38% of patients and 29% of controls. The percentage with migraine without aura was similar in the two groups; thus the current analysis focused only on migraine with aura. ■

ALTERNATIVE MEDICINE

AN EVIDENCE-BASED APPROACH

Riboflavin for Migraine

Rationale for Use

Riboflavin, or vitamin B_2, is a precursor of flavin adenine dinucleotide (FAD), a coenzyme involved in the electron transport aspect of energy metabolism. Some of the support for the use of riboflavin in migraine derives from the observation that FAD deficiency is associated with poor cerebrovascular tone.

The use of this vitamin for migraine prophylaxis is also based on the hypothesis that because impaired mitochondrial metabolism may play a part in pathogenesis, increasing mitochondrial energy efficiency with supplementation might help prevent migraines.

► *The rationale for using riboflavin in migraine prophylaxis is that this vitamin may help improve mitochondrial metabolism.*

► *Studies of riboflavin supplementation have been limited and inconclusive.*

Supplementation with this vitamin has been shown to be beneficial in the treatment of mitochondrial myopathies. In the syndrome involving mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes, patients exhibit reduced mitochondrial metabolism and experience migrainelike headaches.

Clinical Trials

The initial studies of riboflavin were conducted by investigators from the department of neurology at the University of Liege (Belgium). In a randomized trial comparing riboflavin with placebo in 55 patients, significant differences were seen between the treatment and placebo groups in reduction of attack frequency and number of headache days.

Patients whose number of headache days decreased by at least 50% were classified as responders. In the placebo group, 15% were responders, whereas in the riboflavin group 59% were responders (Neurology 1998;50:466-70).

High-dose riboflavin was also evaluated in an open-label, uncontrolled study of 23 patients recruited from a tertiary care center in Berlin. All patients had migraine with or without aura and had had two to eight attacks per month during the 6 months prior to the trial. Twelve of the patients previously had used more than two other types of prophylactic therapies.

After a 4-week baseline period, patients were treated with 400 mg of riboflavin daily for 3 months. Treatment could be extended for an additional 3 months.

Patients kept a headache diary in which they recorded the number and duration of attacks, pain intensity on a 5-point scale, concomitant symptoms, and abortive medications used.

The median attack frequency fell from four to two per month after 3 months of treatment and remained at two after 6 months; these differences from baseline were statistically significant.

The median duration of migraine attacks was 50 hours at baseline. By 6 months, the duration was 28 hours. The median intensity, which was 3.3 at baseline, remained severe, at 3, by 6 months (Eur. J. Neurol. 2004;11:475-7).

A total of 18 patients used triptans to abort migraine attacks. At baseline, these patients used a median of seven tablets per month. This number was significantly reduced to 4.5 tablets per month after 3 months and to 4 tablets per month after 6 months.

Another study, done by clinicians from Kaiser Permanente in California, evaluated a combination product containing 400 mg of riboflavin, 300 mg of magnesium, and 100 mg of feverfew. Both magnesium and feverfew are commonly used by patients with migraine. Magnesium's functions include effects on platelet aggregation, vasospasm, and release of inflammatory mediators, while feverfew inhibits prostaglandin synthetase, 5-lipoxygenase, and cyclooxygenase in leukocytes and serotonin secretion in platelets and polymorphonuclear leukocytes.

Because riboflavin use is associated with bright coloration of the urine, the placebo used in this study included 25 mg of riboflavin, a quantity considered unlikely to have a clinical effect, according to the authors.

On the primary outcome measure, a 50% or greater reduction in the number of migraines after 3 months, there was no difference between the groups: This was achieved by 10 of 24 (42%) and 11 of 25 (44%) of the active treatment and placebo groups, respectively. There also was no difference in the number of patients experiencing a 50% or greater reduction in migraine days, which was achieved by 8 of 24 (33%) and 10 of 25 (40%) of the active treatment and placebo patients, respectively.

Both groups achieved statistically significant reductions, compared with baseline, in the number of migraines. At baseline, both groups had a mean of 5 migraines per month; this number fell to 3.2 in the active treatment group and 3.3 in the placebo group (Headache 2004;44:885-90).

The authors noted that the response rate among the placebo group was higher than that reported in any previous prophylaxis trial; they referred to a meta-analysis in which the percentage of placebo responders ranged from 14% to 34%. In their study, the 44% placebo response rate approached the mean 42% response rate for active treatment, and whether this indicates that the low dose of riboflavin has some clinical efficacy remains unresolved.

The Verdict: Still Out

"Essentially, the supplements were no better than placebo," said Dr. Morris Maizels, who led the Kaiser Permanente study. "There had been some evidence of efficacy for riboflavin, but for magnesium and feverfew there have been as many negative studies as positive studies," he said in an interview. "I think the verdict is still out on these supplements. People practicing headache medicine tend to recommend them for patients who want to avoid side effects, but I've never seen anyone with a dramatic response," Dr. Maizels said.

Dr. Robert A. Bonakdar, director of pain management at the Scripps Center for Integrative Medicine, La Jolla, Calif., said at a symposium on natural supplements that he considers riboflavin to be a well-tolerated agent that can be helpful for patients who do not respond to other prophylactic agents. He suggested that patients be monitored for at least 3-4 months on the 400-mg/day dosage. "For patients who are compliant, there appears to be a lessening in frequency of migraine headaches and a reduced need for abortive medications," he said.

—Nancy Walsh