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Original Article

White Matter Lesions in Children and Adolescents With Migraine

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ABSTRACT

BACKGROUND: The etiology and clinical importance of white matter lesions in migraine remain poorly understood. To understand these issues more fully, we reviewed the brain magnetic resonance imaging scans of pediatric patients and assessed the relationships between white matter lesions, migraine type, patent foramen ovale, and right-to-left shunting. **METHODS:** The magnetic resonance imaging scans of a cohort of children (n = 89) and adolescents, ages 6 to 18 years, who participated in a study of migraine and patent foramen ovale were reviewed. All children in the cohort had undergone saline contrast transthoracic echocardiography and transcranial Doppler studies. **RESULTS:** White matter lesions were detected in 15 of the 89 patients (17%). White matter lesions were small (<5 mm) in the majority (10/15; 66%). We observed no relationship between the presence of white matter lesions and (1) migraine type (six patients with white matter lesions among 35 with migraine with aura [17%] vs. nine with white matter lesions among 54 without aura [17%]; $P = 1.0$); (2) patent foramen ovale (five with white matter lesions among 35 with patent foramen ovale [14%] vs. 10 with white matter lesions among 54 without patent foramen ovale [19%]; $P = 0.77$); or (3) shunt size (two large shunts in 15 with white matter lesions [13%] vs. nine large shunts among 72 without white matter lesions [13%]; $P = 1.0$). **CONCLUSIONS:** These results indicate that small white matter lesions are not infrequent in children and adolescents with migraine. However, no relationships between white matter lesions and migraine type, patent foramen ovale, or degree of right-to-left shunting were observed.

Keywords: white matter lesions, migraine, patent foramen ovale (PFO), MRI, headache

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Background

Several studies indicate that white matter lesions (WMLs) are frequently identified in children and adults with migraine.[1–4] Pathologically, WMLs are foci of ischemic demyelination and gliosis[5,6] that may reflect chronic microvascular damage, potentially facilitated by several factors, including the presence of right-to-left cardiac shunting. Thus, some investigators have suggested that patent foramen ovale (PFO) may participate in the pathogenesis of WMLs in individuals with migraine, especially those with aura. Studies in both children and adults report a higher prevalence of PFO in migraineurs who have aura than in the general population or in migraineurs without aura.[7–9]

Based on these observations, we postulated that WMLs would be more prevalent in children and adolescents with PFO and migraine. To address this hypothesis, we reviewed the brain magnetic resonance imaging (MRI) scans of patients who had participated in an epidemiological study that investigated the prevalence of PFO in pediatric migraineurs and the relationship between migraine subtype, PFO, and right-to-left shunting as measured by transcranial Doppler imaging. This well-characterized cohort of children and adolescents with migraine provided an excellent opportunity

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to gain further insight into the pathogenesis of WMLs in migraine.

Methods

Study population

Children and adolescents with migraine, ages 6 to 18 years, evaluated at the University of Utah/Primary Children's Medical Center (Salt Lake City, Utah) between April 2008 and February 2010, were invited to participate. Primary Children's Medical Center is the major tertiary care center for children living in the Intermountain West, a large geographic region encompassing all of Utah and parts of Wyoming, Idaho, Nevada, Montana, and Colorado. Approximately 2 million infants, children, and adolescents reside in this region. The diagnosis of migraine, with or without aura, was made by the treating pediatric neurologist in accordance with the International Headache Society criteria for pediatric migraine. These diagnoses were subsequently confirmed by two members of the study team (M.S.C., J.F.B.) using the International Headache Society's International Classification of Headache Disorders, 2nd edition.

Neuroimaging studies

MRIs were ordered by the treating neurologist as part of the clinical evaluation for headache; thus, the sample reviewed in this study consisted of a convenience sample of brain MRIs in children with migraine. The MRIs were reviewed independently by two members of the study team (J.F.B., K.R.M.) who were masked to the results of transthoracic echocardiography (TTE) and transcranial Doppler (TCD) studies. Using T2 and fluid-attenuated inversion recovery images and a previously validated rating scale,[10] WMLs, distinct from Virchow-Robin (VR) spaces, were graded based on size (small, $\leq$5 mm; medium, 6-10 mm; or large, $>$10 mm) and location (unilateral, bilateral, localized, or diffuse). Using fluid-attenuated inversion recovery T1 and T2 images, MRIs were evaluated for the number and size of VR spaces and the presence of cerebral infarction or other findings.

Echocardiography and TCD studies

Complete two-dimensional TTE, using agitated saline solution contrast, with and without Valsalva maneuver, was performed on all patients to determine the presence or absence of PFO. Agitated saline contrast transcranial Doppler scans were performed concurrently to determine the size of right-to-left shunting through the PFO. The protocol for TTE and TCD was described previously.[8] Children and adolescents with known congenital heart disease and those unable to cooperate with all studies were excluded. All TTE and TCD studies were reviewed by participating cardiologists (R.T.M., C.B.A., L.L.M.).

Statistical analysis

Demographic data were summarized using descriptive statistics, including percentages, medians, and means. Associations between WMLs and migraine type, PFO, or shunt size were assessed using Fisher's exact test; P values <0.05 were considered significant. The study was approved by the Review Boards of the University of Utah and Intermountain Healthcare (the owner of Primary Children's Medical Center), and written informed consent was obtained from the parents or guardians of participating patients.

Results

Study population

During the study interval, 712 children and adolescents with a primary diagnosis of migraine (International Classification of Diseases 9: 346.xx) were seen in the outpatient clinic by the faculty of the Division of Pediatric Neurology. This included 516 new patients and 196 follow-up patients. In addition, the faculty evaluated 150 children and adolescents (92 new and 58 follow-up) for whom migraine was a secondary diagnosis. An additional 12 patients with migraine were seen during the study interval but not included in the billing records. One patient with migraine had been evaluated by neurology previously and was recruited during a cardiology clinic visit. Of these 875 potential patients with migraine, 139 (15.9%) participated in the study; MRIs, TTEs, and TCDs were obtained in 89 of the 139 patients (64%). In 18 of the 89 patients (20%), MRIs had been obtained by the treating clinician before entry into the study.

Results of MRI studies

WMLs were identified in 15 of the 89 patients (17%; Fig 1); nine of the 15 patients (60%) with WMLs were female. The WMLs were small (i.e., $<$5 mm) in 10 patients, and only one had a WML that exceeded 10 mm in size (Fig 2). WMLs were bilateral in six and unilateral in nine. Six of the 89 imaged patients had transformed migraine, three patients had single episodes consistent with migraine, and one patient each had migraine and a concussion, intercurrent pseudotumor cerebri, migraine variant (intermittent vertigo), or status migrainosus. Of these 13 patients, only one (a 12-year-old boy with intermittent vertigo) had a single WML.

Of the 89 patients, only one had imaging evidence of a cerebral infarction, a remote left middle cerebral artery cerebral infarction. VR spaces, which can be prominent in persons with migraine,[11] were noted in 18 of 89 patients (20%), with 13 patients having five or fewer VR spaces and three patients having between six and 10 VR spaces. Multiple incidental findings were noted, including nonneoplastic cysts (13/89; 15%), brace artifact (9/89; 10%), sinus fluid, inflammation or wall thickening (7/89; 8%), and cerebellar ectopia that did not meet criteria for Chiari malformation (3/89; 3%). Cysts were seen in the

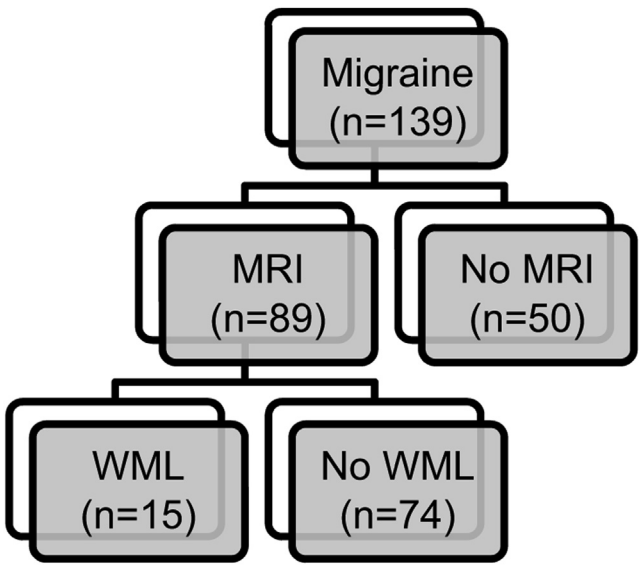

FIGURE 1.
Study flow diagram 139 children and adolescents with migraine had transthoracic echocardiography and transcranial Doppler studies performed. Eighty-nine children in the original study group had brain magnetic resonance imaging (MRI) data available. Fifteen of the patients with migraine and brain MRI data had at least one white matter lesion (WML).