

Opening of the blood-brain barrier preceding cortical edema in a severe attack of FHM type II

Abstract—The authors report a patient with familial hemiplegic migraine type II who developed a long-lasting attack including fever, right-sided hemiplegia, aphasia, and coma. Quantitative analysis of early gadolinium-enhanced MRI revealed a mild but significant left-hemispheric blood-brain barrier (BBB) opening limited to the cortex and preceding cortical edema. The findings suggest that the delayed cortical edema was vasogenic in the severe migraine aura variant of this *ATP1A2* mutation carrier.

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J.P. Dreier, MD; K. Jurkat-Rott, MD; G.C. Petzold, MD; O. Tomkins, MSc; R. Klingebiel, MD; U.A. Kopp; F. Lehmann-Horn, MD; A. Friedman, MD, PhD; and M. Dichgans, MD

Familial hemiplegic migraine (FHM) is a rare mendelian variant of migraine with aura. Delayed cerebral edema is a rare but potentially life-threatening complication of FHM.^{1,2} Its pathogenesis is unknown. Direct evidence is presented here suggesting blood-brain barrier (BBB) opening as its cause.

Methods. Gadolinium-diethylene-triamine-pentaacetic acid (Gd-DTPA) (Magnevist, Schering AG, Berlin, Germany) was used as MRI contrast medium. Quantitative analysis of Gd-DTPA-enhanced MRI was performed as described previously.³ In short, the percent of enhancement values for postcontrast T1-weighted images were calculated from the difference between corresponding voxel average values (16 pixel squares, ~ 2.5 mm²) before and after Gd-DTPA injection using a custom-made Matlab 6.5 script. The resulting image shows brain regions according to the extent of Gd-DTPA accumulation. It was shown previously that the average percentage of enhancement in brain regions protected by the BBB was $3.4\% \pm 1.8\%$. The statistical probability of single postcontrast voxel values greater than 10% was $p < 0.05$ in healthy brain parenchyma (calculated with the Student *t* test for voxel-per-voxel comparison and Bonferroni adjustment for multiple comparison procedures).³

Case report. While working in the hot sun, a 29-year-old male construction worker developed somnolence and headache. Physical examination at admission to the emergency department revealed a patient with global aphasia, right-sided hemiparesis, neck stiffness, and fever ($>39^\circ\text{C}$). C-reactive protein level and leukocyte count were mildly elevated. Cerebral CT (cCT) was normal. Lumbar puncture (LP) was unremarkable apart from a slightly elevated lactate level (23 mg/dL). Serum lactate was normal (14 mg/dL). EEG showed continuous low-amplitude polymorphic delta activity over the left hemisphere but alpha activity over the right. On day 1 after admission, the patient was transferred to the intensive care unit. Gd-DTPA-enhanced T1-weighted MRI revealed meningeal enhancement restricted to the left hemisphere.

Quantitative analysis of Gd-DTPA-enhanced MRI revealed mild but significant enhancement in the left hemispheric cortex (figure, B) whereas T2-weighted images were normal (figure, A). On day 2, a follow-up cCT showed slight effacement of the left hemispheric sulci. Transcranial duplex sonography revealed increased flow velocities and disturbed flow profiles in the left basal cerebral arteries. There was no arterial narrowing on digital subtraction angiography (DSA). The patient's clinical condition deteriorated until day 3 when he developed hemiplegia and was intubated. On that day, repeated MRI demonstrated persistent left hemispheric meningeal enhancement (figure, C) and slight gyral swelling. Diffusion-weighted imaging (DWI) detected no signal abnormalities. On day 4, he showed clinical improvement and was extubated. On day 6, left hemispheric polymorphic delta activity was still present on EEG. On day 9, MRI revealed a pronounced cortical edema on T2-weighted images (figure, D). DWI detected a hyperintensity in the left hemispheric cortex (figure, E), whereas the apparent diffusion coefficient (ADC) maps were unremarkable (figure, F). Meningeal enhancement and BBB opening were still detectable. Transcranial duplex findings had returned to normal. The hemiparesis completely resolved during the following 2 weeks. By that time, EEG predominantly showed one to three per second delta and four to five per second theta activity interspersed with low-amplitude alpha activity over the left hemisphere. Three months later, neuropsychological testing still revealed significant deficits of divided attention (dual-task paradigm, percentile <1.8 misses of critical events), short-term memory, and working memory (Wechsler Memory Scale Revised, percentile 12 digit span forward/percentile five digit span backward), memory for nonverbal information (Rey-Osterrieth Complex Figure Test, percentile 1, delayed recall) and logical reasoning (percentile 8). Neuropsychological testing, EEG, and MRI demonstrated complete recovery at 17 months (figure, G). Medical history revealed two previous aphasia spells lasting for 3 hours. Furthermore, there had been one episode of transient hemiparesis at age 7 months. There was no history of epilepsy but a family history of hemiplegic migraine. Sequencing of the entire coding sequence of the *ATP1A2* gene revealed a heterozygous point mutation (G2704→A) resulting in the amino acid substitution Glu902Lys.⁴ This mutation places a positive charge in a critical region of the protein⁵ and was neither present on 600 control chromosomes nor in unaffected relatives (sister, mother, paternal brother). DNA from the affected parent could not be obtained. We excluded all known *CACNA1A* mutations.

Discussion. Our finding of cortical edema on T2-weighted images in a patient with FHM type II corresponds with a similar observation in two previously reported patients with FHM of whom one had FHM type I.^{1,6} The salient restriction of this edema to the cortical compartment suggests a possible link with the spreading depression theory of migraine aura because spreading depression is expected to propagate in this compartment. Yet the exact mechanisms underlying this edema in FHM are still unknown. Here we propose that if spreading

From the Departments of Neurology (Drs. Dreier and Petzold, U.A. Kopp), Experimental Neurology (Drs. Dreier and Petzold), Neuroradiology (Dr. Klingebiel), Physiology (Dr. Friedman), Charité University Medicine Berlin, Berlin, Germany; Department of Applied Physiology (Drs. Jurkat-Rott and Lehmann-Horn), Ulm University, Ulm, Germany; Department of Neurosurgery (Dr. Friedman, O. Tomkins), Zlotowski Center for Neuroscience, Ben-Gurion University, Beersheva, Israel; and Department of Neurology (Dr. Dichgans), Klinikum Grosshadern, Ludwig-Maximilians-University, Munich, Germany.

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Address correspondence and reprint requests to Dr. Jens P. Dreier, Department of Neurology, Charité Campus Mitte, Charité University Medicine, Schumannstr. 20/21, 10117 Berlin, Germany; e-mail: jens.dreier@charite.de

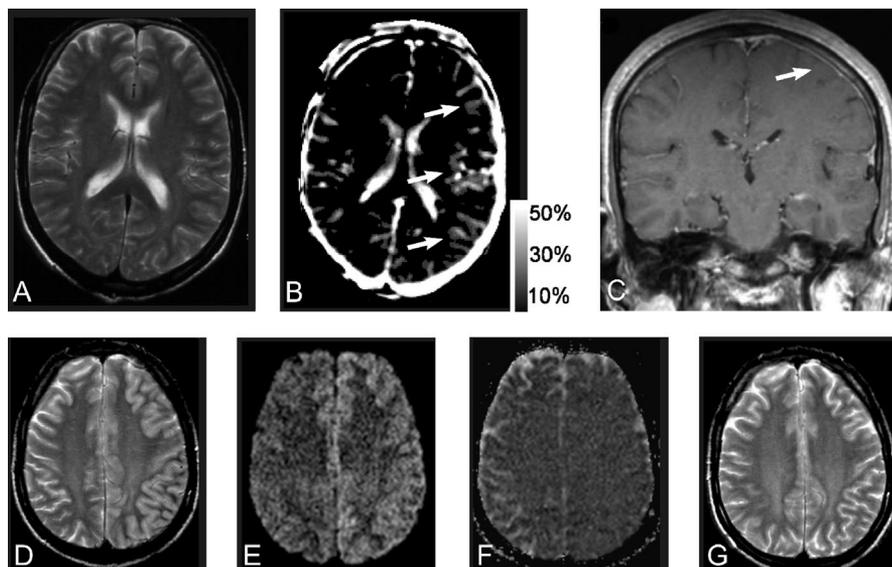


Figure. Cerebral MRI study on day 1 after symptom onset. (A) Normal T2-weighted image. (B) Quantitative analysis of gadolinium-diethylene-triamine-pentaacetic acid (Gd-DTPA)-enhanced MRI. Gray scale-coded percentage enhancement values for the T1-weighted image after Gd-DTPA injection compared with the image before Gd-DTPA are demonstrated. Note the significant enhancement of the left hemispheric cortex band (white arrows), where the edema evolved later on. Cortical enhancement was most prominent in the temporo-occipital lobes. Particularly note the enhancement in the perisylvian cortex where language skills are represented, which showed a delayed recovery. (C) Postcontrast T1-weighted coronal image shows dural enhancement restricted to the left hemisphere (white arrow, day 3). (D to F) Cerebral MRI studies on day 9. (D) Pronounced cortical edema on T2-weighted image. (E) Left hemispheric hyperintensity was detected on a diffusion-weighted imaging (DWI) slice (b 1,000 s/mm^2) within the cortex (F), whereas the apparent diffusion coefficient map was unremarkable, suggesting vasogenic rather than cytotoxic edema (T2 shine through phenomena of DWI). (G) Follow-up MRI 17 months later: Regular signal intensities are seen on the T2-weighted image. There is no evidence of cortical atrophy consistent with vasogenic rather than cytotoxic edema.

depression causes this migraine aura variant, spreading depression may open the BBB, which, in turn, leads to extravasation of serum protein and consequent vasogenic edema.

Gd-DTPA does not cross the intact BBB and post-contrast T1-weighted imaging in animal models correlated with the degree of BBB opening.⁷ Based on these findings, Gd-DTPA is used routinely in patients to demonstrate noninvasively and qualitatively BBB opening. Quantitative analysis, as applied here, has been shown previously to increase the sensitivity of this technique. Generalized enhancement correlated with increased CSF albumin concentrations.³ Although significant, the BBB opening in our patient was mild, consistent with the slow edema development. The CSF/serum albumin quotient showed an insignificant increase over the first week from 4.5 to 5.2×10^{-3} . The delayed DWI signal abnormalities were unlikely related to cytotoxic edema; rather they were vasogenic, reflecting inherent T2 properties of DWI (T2 shine through phenomena) because ADC maps with pure diffusion characteristics without T2 effects remained normal. In animal experiments, evidence linking spreading depression with BBB opening and vasogenic edema was recently shown to be related to matrix metalloproteinase up-regulation.⁸ We found evidence of BBB opening in our patient approximately 24 hours after symptom onset, corresponding with the time course of BBB opening in animals after spreading depression.⁸

The time course of the cortical edema suggested that it was not involved in the pathogenesis of the initial headache and neurologic deficits in our patient. However, the edema may have contributed to his delayed recovery. Consistently, in animals, isolated BBB opening and vasogenic edema produced delayed activation of astrocytes followed by altered glutamatergic and GABAergic neurotransmission lasting for at least 6 weeks. This was limited to the cortical area where the BBB was open.⁹

The clinical course over the first 48 hours showed a progressive fluctuating deterioration. Similar protracted clinical courses have been observed in FHM type I.^{1,2} An obvious interpretation of the fluctuations could be a status aurae migraenalis, i.e., if spreading depression causes this syndrome, a spreading depression status as observed for spreading depression-like depolarizations in patients after head trauma.¹⁰ The *ATP1A2* mutation could promote this status by reducing the spreading depression threshold. Speculatively, the actual spreading depression trigger was an exertional heat stroke in our patient. Interestingly, the beginning of the clinical recovery coincided with the intubation, which raises the possibility that the sedative (Disoprivan [propofol]) may have inhibited spreading depression recurrence.

The unilateral dural enhancement was consistent with the concept of neurogenic inflammation in migraine. The MRI was performed after LP. Although it cannot be excluded that this procedure contributed to the meningeal contrast enhancement, the LP alone cannot explain the isolated involvement of the left hemisphere.

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Correction

Generalized arteriopathy in patients with cervical artery dissection

In the article “Generalized arteriopathy in patients with cervical artery dissection” (*Neurology* 2005;64:1508–1513) by Völker et al., the affiliations footnote was incorrect. The corrected affiliation should be as follows:

From the Institute of Atherosclerosis Research (Drs. Völker, Ringelstein, and Kuhlenbäumer); Department of Neurology (Drs. Besselmann, Dittrich, Nabavi, Konrad, Dziewas, Evers, Stögbauer, Ringelstein, and Kuhlenbäumer), Department of Psychiatry (Dr. Konrad), Department of Ophthalmology (Dr. Grewé), and Department of Radiology (Drs. Krämer and Bachmann), University of Münster, Münster, Germany.

The authors apologize for the error.

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