Younis et al. Glutamate levels and perfusion in pons during migraine attacks: a 3 tesla MRI study using proton spectroscopy and arterial spin labeling

Supplementary material

Definition of pharmacologically induced migraine-like attacks

The headache questionnaire included information on pain intensity based on a numeric rating scale (range 0–10; from no pain to worst imaginable pain), location of headache, aggravation by physical activity, associated symptoms (nausea and/or vomiting, sensitivity to light and sounds) and whether the headache mimicked the patients' usual attacks.

Modified criteria were used to define migraine-like attacks as pharmacologically induced attacks are not spontaneous and cannot per se fulfill the criteria of the beta version of the third International Classification of Headache Disorders (ICHD-3 beta).[1] Modified criteria were developed based on the three following considerations. Firstly, the majority of patients report that pharmacologically induced attacks mimic their usual spontaneous attacks.[2,3] Secondly, a spontaneous migraine attack commonly develops in a matter of hours, and during this time it phenomenologically only fulfill the criteria for tension-type headache. Hereafter, the headache worsens, becomes unilateral and displays associated symptoms, required for a migraine diagnosis. Thirdly, most patients are capable of predicting an impending migraine in the early stage of the attack and cannot be denied acute migraine medication in a research study. Consequently, induced migraine attacks are often treated before all criteria are fulfilled. Based on these considerations, we applied the modified criteria to define a migraine attack in our study:[4,5]

(i) Headache fulfilling ICHD-3 beta criteria C and D for migraine without aura:

C. Headache has at least two of the following characteristics: unilateral location, pulsating quality, pain intensity ≥ 4, aggravation by cough (in-hospital phase) or causing avoidance of routine physical activity (out-hospital phase).

D. At least one of following during headache: nausea and/or vomiting; photophobia and phonophobia.

(ii) Headache described as mimicking patient's usual attacks and effectively aborted with acute migraine medication. Treatment efficacy was defined as ≥ 50% decrease in pain intensity within 2 h.

MR data acquisition and post-processing

Structural imaging

Anatomical parameters for the 3D T1-weighted turbo field echo sequence were: field of view 240 × 240 × 170 mm3, voxel size 1.00 × 1.08 × 1.10 mm^3, echo time 3.7 ms, repetition time 8.0 ms and flip angle 8°. Images were segmented into gray matter, white matter and cerebrospinal fluid using the FSL-functions BET and FAST (Version 5.0.10, FMRIB Software Library, University of Oxford, Oxford, UK).

Proton magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (^{1}H-MRS) sequence parameters were: VOI size 10.5 × 12.5 × 22 mm^3, repetition time 3000 ms, echo time 38.3 ms and 480 acquisitions with a duration of 24 min. Water concentration in each acquired VOI was estimated based on the content of gray matter, white matter and cerebrospinal fluid in the VOI, obtained from the segmentation of anatomical images.[6] ^{1}H-MRS protocol was optimized to target small deep brain areas and reduce potential partial volume effects by using small VOI and increased acquisitions number.

Unsuppressed water signal was obtained from VOI as an internal reference for quantifying metabolites.[7]

Pseudo-continuous arterial spin labeling

Multi inversion times 2D arterial spin labeling sequence with a pseudo-continuous labeling duration of 1650 ms and 7 post-labeling delays (TI1/ΔTI =100ms/300ms) was acquired using a Look-Locker scheme with an echo planar imaging read-out. Sequence parameters were: 13 axial slices, field of view 220 × 220 × 78.6 mm^3, voxel size 3.44 × 3.44 × 6.6 mm^3, repetition time 3000 ms, echo time 11 ms, flip angle 40° and slice readout duration 22 ms. The slices covered the brain from lower pons and up (except cortical area above corpus callosum).

Post-processing was performed in BASIL (part of FSL), where default values for pseudo-continuous arterial spin labeling (pCASL) were used, adding only information of bolus duration, post-labeling delay, slice timing difference, and Look-Locker flip-angle. CBF maps were acquired by registration of pCASL data to corresponding anatomical images of each scan session using boundary-based registration (FLIRT, part of FSL). Anatomical images were subsequently registered to MNI-152 standard 2 mm brain using a non-linear warp (FNIRT, part of FSL). Visual inspection of registration to the anatomical image and MNI-152 space was performed to assure good registration. pCASL signal was normalized to a mean, partial volume corrected, grey matter value, based on the brain tissue type segmentation of anatomical images.

Phase-contrast mapping

Fast 2D inflow angiogram was acquired before phase-contrast mapping (PCM) for visualization of basilar and carotid arteries and positioning of PCM sequences. Sequence parameters for the fast 2D angiogram, used for PCM, were: field of view 200 × 150 × 200 mm^3, acquired matrix size

200 × 134 mm, acquired voxel resolution 1.00 × 1.5 × 2.00 mm^3, reconstructed resolution 0.39 × 0.39 × 1.00 mm^3, repetition time 23 ms, echo time 3.5 ms, flip angle 18°, SENSE p reduction 2, and duration 2 min 46 sec. Parameters of the turbo field echo PCM sequence were: field of view 240 × 240 mm^2, voxel size 0.75 × 0.75 × 8 mm^3, 1 slice, repetition time 12.7 ms, echo time 7.72 ms, flip angle 10°, 10 repeated measures, velocity encoding (100 cm/s) without cardiac gating, and scan duration of 1 minute 50 seconds. Two blood velocity maps were acquired with imaging planes placed orthogonal to both carotid arteries and basilar artery, respectively. Total blood flow to the brain was calculated by drawing ROIs covering the three arteries, as described previously,[8] by the same investigator (SY) blinded for subject, scan order and drug. Quantitative global CBF values (mL/100 g/min) were calculated by normalizing total blood flow to individual whole brain tissue weight acquired from segmented anatomical images, excluding cerebrospinal fluid, and assuming a brain density of 1.05 g/ml.[9] All post-processing was performed using in-house developed and validated MATLAB scripts.[8]

Supplementary references

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