The Association Between Clinical Characteristics of Migraine and Brain GABA Levels: An Exploratory Study

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Abstract: Migraine is prevalent and disabling yet is poorly understood. One way to better understand migraine is to examine its clinical characteristics and potential biomarkers such as gamma-aminobutyric acid (GABA). The primary objective of this study was to explore whether relevant disease characteristics of migraine are associated with brain GABA levels. Twenty adults fulfilling the established diagnostic criteria for migraine and 20 age- and gender-matched controls completed this cross-sectional study. Pain, central sensitization, negative emotional state, and perceived disability were measured using Short-form McGill Pain Questionnaire-2, Central Sensitization Inventory, Depression Anxiety Stress Scales-21, and Headache Impact Test-6, respectively. Secondary analysis of brain GABA levels of the same cohort measured using proton magnetic resonance spectroscopy was conducted. The migraine group had significantly higher scores than the control group on pain, central sensitization, and disability. Correlation analyses showed fair positive association between GABA levels and pain and central sensitization scores. No association was found between GABA levels and emotional state and disability. These findings are preliminary evidence supporting the use of questionnaires and GABA levels in characterizing migraine better and broadening the diagnostic process. These findings also strengthen the rationale for the role of GABA in migraine pathophysiology and corroborate the potential of GABA as a migraine biomarker.

Perspective: Higher pain and central sensitization scores were associated with increased brain GABA levels in individuals with migraine. These findings offer preliminary evidence for the usefulness of measuring pain and central sensitization in migraine and provide some support for the possible role of GABA in migraine pathophysiology and its potential as a diagnostic marker.

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Key words: Gamma-aminobutyric acid, migraine disorders, headache, central sensitization, disability, questionnaires.
system and is an important regulator of the balance between excitation and inhibition in the brain. As such, GABA has been implicated in clinical conditions thought to involve an imbalance between excitatory and inhibitory processes. Interestingly, recent studies have also implied that GABA mediates excitatory actions as well, for example in the development of epilepsy. We have recently published findings that brain GABA levels are significantly higher in people with migraine compared with age- and gender-matched control subjects and have shown that GABA has good diagnostic potential for migraine. These findings were the first direct evidence for the putative role of GABA in migraine and its potential as a migraine biomarker. Following the 3-stage model suggested by Hlatky and colleagues to validate biomarkers, it is then necessary to establish migraine characteristics associated with GABA and finally to determine that screening using the biomarker leads to targeted treatment and eventually reduces disease burden. The second stage of validation might be furthered by exploring associations of GABA levels with pain, central nervous system sensitization, negative emotional state, and disability. The primary aim of this study was to explore whether relevant clinical characteristics of migraine including pain, central nervous system sensitization, emotional state, and headache-related disability are associated with GABA levels. A secondary aim of this study was to compare clinical characteristics, particularly central nervous sensitization and emotional state, between people with migraine and asymptomatic control participants. By exploring the relationship of clinical characteristics with GABA levels, we aim to build on the process of validating GABA as a migraine biomarker, inform migraine diagnosis, and better understand migraine.

Methods

Design

A secondary analysis of a previous cross-sectional case-control study that compared GABA levels between people with migraine and age- and gender-matched control participants was performed to explore the association between GABA levels and migraine clinical characteristics. This research was granted ethics approval by the Human Research Ethics Committee of the University of Sydney (Project Number 2012/581).

Participants

Participants with migraine were eligible for the original study if they were diagnosed with migraine by their attending neurologist/physician and if their headache features fulfilled the International Classification of Headache Disorders (ICHD)-II criteria for migraine. Participants in the control group were included if they did not experience recurrent headaches, had never experienced a migraine episode, and were not experiencing significant pain nor pain longer than 3 months at the time of the study. Participants in the control group were matched to the migraine group for age and gender. Participants in both groups were excluded if they used medications known to alter GABA levels. Complete inclusion and exclusion criteria and other details of participant recruitment are described elsewhere. In brief, participants were recruited through advertisements posted at university, consumer support groups, and primary care sites.
**Procedures**

We conducted initial telephone screening of potential participants to determine their eligibility. All participants in the migraine group then underwent an interview and physical examination to confirm classification according to ICHD-II criteria and to exclude headache participants with nonmigrainous or mixed classification headache. Control participants were also interviewed and physically examined.

Participants with migraine provided information on headache characteristics including history of migraine, frequency of episodes, typical duration of each migraine episode, and headache intensity in the past month using the visual analogue scale (with anchors at 0 and 10: 0 = no pain, 10 = worst pain possible). In addition, participants described the location of their headache, associated symptoms, and any medication and/or treatment received.

All participants satisfying the inclusion and exclusion criteria completed self-administered paper-and-pen questionnaires that were arranged in a standardized manner to ensure consistency. Questionnaires, described in the section Clinical Characteristics on the Basis of the Self-Report Questionnaires, included information about pain and central nervous system sensitization experience, emotional state, and disability. Completed questionnaires were checked for any misunderstood or inadvertently missed item. Participants then underwent proton magnetic resonance spectroscopy to determine brain GABA levels. All participants provided written informed consent before participation.

**Outcomes**

**Brain GABA Levels**

Brain GABA levels were measured in institutional units using single-voxel proton magnetic resonance spectroscopy using the Mescher-Garwood point resolved spectroscopy sequence (repetition time = 1800 ms; echo time = 68 ms; number of excitations [phase cycling], 8; number of acquisitions, 256; number of points, 4096; spectral width, 5000; voxel size, $3 \times 3 \times 3 \text{ cm}^3$; total scan time, 8 minutes 24 seconds). The voxel was positioned lateral to the midline posterior cingulate, and posterior and superior to the splenium of the corpus callosum (Fig 1). Spectroscopy was performed during the interictal period for participants in the migraine group; no one had migraine-related symptoms on the day of testing. Details of the full spectroscopy methods and parameters are reported elsewhere.

**Clinical Characteristics on the Basis of the Self-Report Questionnaires**

Migraine pain characteristics were described using the Short-form McGill Pain Questionnaire-2 (SF-MPQ-2) comprised of 22 pain quality descriptors scored for intensity on a 0 to 10 Likert scale. SF-MPQ-2 has been validated for use for neuropathic pain, as is thought to be present in migraine. For this study, the top and bottom quartiles of intensity scores were considered to reflect the words that people with migraine used the most and least, respectively, to describe their headache. SF-MPQ-2 also provided information on the multidimensional nature of the migraine pain experience by generating summary scores for continuous, intermittent, neuropathic, and affective pain subscales, aside from the total SF-MPQ-2 scores.

Presence of symptoms of central nervous system sensitization was measured using the Central Sensitization Inventory (CSI). The CSI is a highly reliable and valid screening tool for central sensitivity syndromes, that is, diseases that have central sensitization as a common feature. Scores of ≥40 indicate possible central sensitivity syndromes, with higher CSI scores reflecting a higher degree of sensitization. CSI discriminates people with central sensitivity syndromes, including migraine, from those without pain, with sensitivity = 81% and specificity = 75% and from those with chronic pain without central sensitivity symptoms (sensitivity = 83%; specificity = 55%).

![Figure 1. Placement of the single voxel in the (A) axial, (B) coronal, and (C) sagittal planes for proton magnetic resonance spectroscopy analysis.](image-url)
Emotional state was measured using the Depression Anxiety Stress Scales-21 (DASS-21). The DASS-21 is a short, valid, and highly reliable instrument providing depression, anxiety, and stress scores on the basis of frequency and severity of symptoms. It has been used to investigate the association of negative emotional state with migraine. Perceived levels of disability were measured using the Headache Impact Test-6 (HIT-6), a brief questionnaire on the effect of the headache on work and daily activities. The HIT-6 was shown to have high reliability and good validity in discriminating migraine from other headaches.

Statistical Analyses

Spearman $\rho$ and Kendall $\tau$ correlations were used to explore associations between GABA levels and normally and non-normally distributed clinical characteristics, respectively, in individuals with migraine. Correlation coefficients were interpreted as follows: >.75, good to excellent relationship; .50 to .75, moderate to good relationship; .25 to .50, fair relationship; and .00 to .25, little or no relationship. These correlation analyses were performed after normality of the distribution of data was tested using the Shapiro–Wilk statistic.

We conducted area under the receiver operating characteristic (ROC) curve analysis for clinical characteristics that had at least a fair association with GABA levels and that might be useful in discriminating migraine. To this end, we computed for optimal cutoff value, area under the curve, sensitivity, and specificity of the questionnaire score. On the basis of these calculations, we interpreted diagnostic accuracy to be excellent, good, fair, or poor.

Descriptive statistics (frequency, mean and SD, median and interquartile range) of headache characteristics and self-report questionnaire scores were used to report clinical characteristics. The Wilcoxon signed rank test was used to determine differences in clinical characteristics on the basis of questionnaire scores between migraine and control groups because not all were normally distributed. Pairs were excluded from analysis if either case or control data were missing. Glass $\Delta$ was calculated to compare the difference between mean scores of the migraine and control groups.

Statistical analyses were conducted using Statistical Package for Social Sciences statistical software, version 21 (SPSS Inc, Chicago, IL) for Windows. Significance level was set at .05.

Because this was an exploratory study using secondary analysis of brain GABA levels from a previous cross-sectional case-control study, the sample size of the present study was on the basis of that of the previous study ($n = 40$). This sample size was powered to detect group differences in brain GABA levels.

**Results**

**Participants**

Twenty people with migraine and 20 age- and gender-matched control subjects participated in this study. The median age (interquartile range) of the migraine group was 33 (28–47) years and the median age (interquartile range) of the control group was 30 (26–48) years. Fourteen of 20 participants (70%) of each group were women. The average duration of migraine symptoms was 15 years, with a frequency of 3 to 5 times per month (Table 1). Migraine characteristics of the participants (Table 1) were consistent with the ICHD diagnostic criteria for migraine. Most participants reported more than 1 location of headache, with 85% reporting temporal location and 80% reporting frontal location (Fig 2). Participants most commonly chose aching (95%), tiring-exhausting (80%), throbbing (75%), sickening (70%), and sharp (65%) from the SF-MPQ-2 to describe their headaches (Fig 3). More than half of the participants with migraine (55%) were not taking migraine medications at the time of assessment and had neither
sought physical treatment such as physiotherapy nor alternative treatment such as acupuncture (Table 1).

Of all the variables considered, only the following variables were normally distributed: history of migraine, intensity of headache in the past month, and scores on HIT-6, CSI, SF-MPQ-2-continuous, SF-MPQ-2-affective, and SF-MPQ-2 total scores.

**Association Between Clinical Characteristics and GABA Levels Among People With Migraine**

There was fair positive association between GABA levels and pain scores, specifically total SF-MPQ-2 scores ($r = .47; P = .04$) and SF-MPQ-2 scores on intermittent ($\tau = .33; P = .04$), neuropathic ($\tau = .37; P = .03$), and affective ($\rho = .49; P = .03$) pain subscales (Table 2 and Fig 4A). There was also fair positive association between GABA levels and scores on the CSI ($\rho = .48; P = .03$; Fig 4B). GABA levels were not associated with headache history, frequency, duration, or intensity, continuous pain domain on the SF-MPQ-2, depression, anxiety, and stress scales of DASS-21, nor levels of disability ($P > .05$; Table 2).

Of the variables having fair association with GABA levels, only CSI scores were suitable for ROC analysis because the migraine and the control groups had scores >0 on the CSI. Results of this analysis revealed that CSI appears to have good accuracy for classifying individuals as having migraine or not (area under the curve = .88; 95% confidence interval,.76–1.00; $P < .001$; Fig 5). The optimal CSI cutoff score to distinguish people with migraine from those who do not get regular headaches was 22.5, with sensitivity of 95%, specificity of 80%, and positive likelihood ratio of 4.75.

**Clinical Characteristics of Migraine and Control Groups on the Basis of Self-Report Questionnaires**

There were significant differences between groups for scores on all of the self-report questionnaires (Table 3). The 2 groups differed the most in their scores on HIT-6, SF-MPQ-2 continuous pain, and CSI, as shown by their

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**Figure 3.** Top and bottom 5 pain descriptors chosen by participants with migraine to describe their headaches (n = 20).

**Table 2.** Association of GABA Levels and Clinical Characteristics of Migraine Using Spearman $\rho$, or Kendall $\tau$, Correlation Coefficient ($P$ Values)

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>GABA LEVEL, CORRELATION COEFFICIENT ($P$)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache characteristics</td>
<td></td>
</tr>
<tr>
<td>Migraine history</td>
<td>$\rho = -.40$ (.08)</td>
</tr>
<tr>
<td>Frequency of headache in a month</td>
<td>$\tau = .16$ (.33)</td>
</tr>
<tr>
<td>Episode duration</td>
<td>$\tau = -.01$ (.94)</td>
</tr>
<tr>
<td>Average headache intensity last month</td>
<td>$\rho = .17$ (.48)</td>
</tr>
<tr>
<td>Pain and sensitization</td>
<td></td>
</tr>
<tr>
<td>SF-MPQ-2 total score</td>
<td>$\rho = .47$ (.04)</td>
</tr>
<tr>
<td>SF-MPQ-2 continuous pain score</td>
<td>$\rho = .21$ (.38)</td>
</tr>
<tr>
<td>SF-MPQ-2 intermittent pain score</td>
<td>$\tau = .33$ (.04)</td>
</tr>
<tr>
<td>SF-MPQ-2 neuropathic pain score</td>
<td>$\tau = .37$ (.03)</td>
</tr>
<tr>
<td>SF-MPQ-2 affective descriptors</td>
<td>$\rho = .49$ (.03)</td>
</tr>
<tr>
<td>CSI total score</td>
<td>$\rho = .48$ (.03)</td>
</tr>
<tr>
<td>Emotional state</td>
<td></td>
</tr>
<tr>
<td>DASS-21 depression score</td>
<td>$\tau = -.14$ (.42)</td>
</tr>
<tr>
<td>DASS-21 anxiety score</td>
<td>$\tau = .17$ (.34)</td>
</tr>
<tr>
<td>DASS-21 stress score</td>
<td>$\tau = -.13$ (.43)</td>
</tr>
<tr>
<td>Disability (HIT-6 score)</td>
<td>$\rho = .06$ (.79)</td>
</tr>
</tbody>
</table>

* Spearman $\rho$, Kendall $\tau$.

(Correlation is significant at the .05 level (2-tailed).)

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respective Glass Δ. Notably, there was no statistically significant between-group difference for the anxiety scale of DASS-21. Participants from both groups had scores categorized as “normal” for this scale.

Discussion

Our results show that pain and central sensitization scores had a fair positive association with GABA levels in participants with migraine. These results support a putative role for GABA in migraine pathophysiology particularly when migraine presents with moderate to severe headache and central nervous system sensitization. This association between these migraine features and GABA also provides some further support in validating GABA as a potential biomarker for migraine.

GABA levels were associated with 3 of the 4 summary scales of pain quality and severity contained in the SF-MPQ-2, namely intermittent, neuropathic, and affective pain. People with higher pain scores on SF-MPQ-2 scores tended to have higher GABA levels. These results give rise to the question whether the observed relationship between GABA levels and pain scores are characteristic of migraine or of any pain condition. We believe that the association between increased GABA levels and higher pain scores indicates a change in brain chemistry specific to migraine or chronic episodic headache for 3 reasons. First, we measured GABA levels during the interictal period, when participants were free of headache. Second, 2 participants in the control group had mild pain in the limb. Third, increased GABA levels in people with migraine oppose the decreased GABA levels reported in other pain conditions from previous studies, although measured from different brain regions (from the insula in fibromyalgia and thalamus in people with spinal cord injury with neuropathic pain compared with those without neuropathic pain). The association between GABA levels and pain scores also implies that SF-MPQ-2 may be used as a basis for inferring about GABA levels when spectroscopy data are unavailable. Interestingly, GABA levels were not associated with headache intensity on the basis of participant rating of their usual headaches. We speculate that the difference in findings is because participants considered pain differently when presented with words on the SF-MPQ-2 than when asked to rate their usual headaches. Using the

Figure 4. Scatter plot with regression line showing positive association between brain GABA levels and scores on the (A) SF-MPQ-2 ($r = .47; P = .04$) and (B) CSI ($r = .48; P = .03$) in the migraine group ($n = 20$).

Figure 5. ROC curve evaluating CSI scores of people with migraine and control subjects. Area under the curve = .88 (95% confidence interval, .76–1.00); $P < .001$. 
Increased GABA levels were associated with higher central sensitization scores. This means that increased GABA levels are most likely to be higher when central sensitization symptoms are more frequent. One possible explanation for this relationship may be the role of GABA in regulating excitatory-inhibitory balance in the brain. The increased GABA levels in people with migraine may cause abnormal excitability of the trigeminovascular system, as previously postulated for migraine (interictal period) and also possibly because our participants were more homogenous with generally more frequent and more severe headaches than the cohort reported on by Bigal and colleagues.

The homogeneity of headache characteristics of the migraine cohort was ideal for investigating potential disease biomarkers and therefore was one of the strengths of this study. We also believe that we were able to detect an association between GABA and pain and central sensitization partly because GABA levels were measured from the cingulate cortex, previously shown to have altered functioning in pain states. Localizing the voxel in this region also allowed the use of a large voxel to maximize signal-to-noise ratio for GABA. Although this study provides new insights on migraine characterization and the role of GABA in pathophysiology, some limitations should be considered. First, GABA levels were measured from just 1 region to achieve good signal quality in a short acquisition time. We do not know if increased GABA levels, and therefore their association with clinical characteristics, are different in other brain regions. Second, spectroscopy was done during the interictal period so it is not possible to tell if GABA levels are also increased during the ictal period. It seems lower than the previously reported CSI cutoff score of 40 to identify central sensitization syndromes, suggesting the possible specific use of the CSI for migraine identification. The CSI provides information beyond ICHD criteria and therefore broadens the diagnostic process and enhances the clinician’s appreciation of the patient’s experience.

SF-MPQ-2, participants rated the intensity associated with the specific words. However, when asked to rate the intensity of their usual headaches, participants could be thinking of the whole headache experience, how the headache affected their lives, or how long they had been dealing with the symptoms.

Increased GABA levels were associated with higher central sensitization scores. This means that increased GABA levels are most likely to be higher when central sensitization symptoms are more frequent. One possible explanation for this relationship may be the role of GABA in regulating excitatory-inhibitory balance in the brain. The increased GABA levels in people with migraine may cause abnormal excitability of the trigeminovascular system, as previously postulated for migraine. This explanation is plausible because most of the participants reported having photophobia and/or phonophobia, both considered clinical expressions of sensitization. We have previously reported that glutamate and glutamine measured from the same cohort did not differ between the migraine and control groups. These findings support the role of increased GABA in the altered excitability of the brain. Another possible explanation for the relationship between increased GABA levels and higher sensitization is on the basis of the role of GABA in neurovascular coupling. GABA has been shown previously to cause vasodilation during neurovascular coupling where cortical blood flow adjusts according to cortical activity. Neurovascular coupling may be impaired in people with migraine, leading to the progression of migraine symptoms. Therefore, the relationship between increased GABA levels and higher central sensitization scores may also be indicative of a role for GABA in migraine symptoms. Further, results of ROC curve analysis indicate that people with CSI scores of 22.5 are nearly 5 times more likely to have migraine than those with scores below this. This cutoff score is

### Table 3. Comparison of Clinical Characteristics on the Basis of Self-Report Questionnaires Between Migraine and Control Groups (n = 40)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Migraine (n = 20)</th>
<th>Control (n = 20)</th>
<th>Glass Δ</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain and sensitization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-MPQ-2 total score</td>
<td>2.2 (1.5)</td>
<td>3.3 (1.6)</td>
<td>.006</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SF-MPQ-2 continuous pain score</td>
<td>3.7 (2.0–4.4)</td>
<td>2.3 (2.3)</td>
<td>.005</td>
<td>.095</td>
</tr>
<tr>
<td>SF-MPQ-2 intermittent pain score</td>
<td>1.7 (–3.2)</td>
<td>.9 (1.2)</td>
<td>.005</td>
<td>.006</td>
</tr>
<tr>
<td>SF-MPQ-2 neuropathic pain score</td>
<td>.0 (0–0)</td>
<td>.0 (0–0)</td>
<td>.006</td>
<td>.006</td>
</tr>
<tr>
<td>CSI total score</td>
<td>35.0 (9.6)</td>
<td>32.0 (30–42.5)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td><strong>Emotional state</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DASS-21 depression score</td>
<td>3.4 (3.9)</td>
<td>3.1 (3.6)</td>
<td>.005</td>
<td>.009</td>
</tr>
<tr>
<td>DASS-21 anxiety score</td>
<td>3.1 (3.6)</td>
<td>3.1 (3.6)</td>
<td>.005</td>
<td>.009</td>
</tr>
<tr>
<td>DASS-21 stress score</td>
<td>9.2 (8.2)</td>
<td>9.2 (8.2)</td>
<td>.006</td>
<td>.006</td>
</tr>
<tr>
<td><strong>Disability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIT-6 total score*</td>
<td>61.6 (7.6)</td>
<td>63.0 (57.2–65.5)</td>
<td>.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range. Note: Bold numbers indicate statistical significance (P < .05).

*HIT-6 scores range from 36 to 78; a score <49 indicates little or no effect (grade 1); a score of 50 to 55 indicates moderate effect (grade 2); a score of 56 to 59 indicates substantial effect (grade 3), and score ≥60 indicates severe effect (grade 4).
reasonable to speculate, however, that GABA levels might also be altered if measured during the ictal period. This speculation is on the basis of a previous proposal that the brain in people with migraine changes in function and structure over time due to repeated migraine episodes. These changes may include a dysregulation of the excitatory-inhibitory balance in the brain involving GABA. Correspondingly, we speculate that GABA levels measured during the ictal period might also be associated with symptoms of central sensitization and pain. Third, this study was intended to be exploratory and therefore was not set up for multivariate analyses and adjustment for multiple comparisons. For the same reason, we did not design the study to include the presence or absence of aura symptoms nor the varied medications of the participants as covariates in the analyses. Last, DASS-21 and HIT-6 scores of our participants had insufficient variability for rigorous analysis.

Further studies are therefore required to confirm the results of our study. Larger, longitudinal cohort studies may investigate the association between GABA levels and clinical characteristics in migraine and other headache types during the ictal and interictal periods. Additional factors that may be related with GABA levels in migraine may be investigated such as other neurotransmitters, presence or absence of aura, and medications. Similarly, it will be useful to determine whether questionnaires can differentiate migraine from other headache types. Further studies can also build on results of this study to validate GABA as a biomarker and address the lack of established biomarkers for migraine. Nevertheless, results of this study strengthen the rationale for the role of GABA in migraine pathophysiology and thus add to the understanding of migraine. The association of pain and central nervous system sensitization symptoms with GABA levels in migraine suggests that patients’ subjective reports correlate with brain chemistry. Hence, assessing these clinical characteristics using the SF-MPQ-2 and CSI is useful, and allows for more specific characterization of migraine. It is hoped that a better understanding of migraine will eventually pave the way for effective targeted treatment options.

Conclusions

Increased GABA levels were associated with increased pain and more frequent central sensitization symptoms in people with migraine. These findings contribute to the understanding of migraine. These findings also provide early evidence for the usefulness of measuring GABA and pain and central sensitization in characterizing migraine better and broadening the diagnostic process. In addition to enhancing diagnosis and assessment, using self-report questionnaires in clinical practice may facilitate understanding of a patient’s headache experience. This new information on the association of clinical characteristics of GABA levels in migraine brings us a step closer to showing the validity of GABA as a migraine biomarker.

Acknowledgments

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