ARTICLE

Correlation of neurochemical and imaging markers in migraine

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PACAP38 and DTI measures

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Abstract

Objective

To examine whether interictal plasma pituitary adenylate cyclase-activating peptide 38-like immunoreactivity (PACAP38-LI) shows correlation with the microstructural integrity of the white matter in migraine.

Methods

Interictal plasma PACAP38-LI was measured by radioimmunoassay in 26 patients with migraine (24 women) who underwent diffusion tensor imaging afterward using a 1.5-tesla magnetic resonance scanner. Data were analyzed using tract-based spatial statistics included in FMRIB's Software Library.

Results

Interictal plasma PACAP38-LI showed significant correlation with mean diffusivity ($p < 0.0179$) mostly in the bilateral occipital white matter spreading into parietal and temporal white matter. Axial and radial diffusivity showed positive correlation with interictal PACAP38-LI ($p < 0.0432$ and $p < 0.0418$, respectively) in the left optic radiation and left posterior corpus callosum. Fractional anisotropy did not correlate significantly with PACAP38-LI. With disease duration as a nuisance regressor in the model, PACAP38-LI correlated with axial and mean diffusivity in the left thalamus ($p < 0.01$).

Conclusion

We report a link between PACAP38, a pathobiologically important neurochemical biomarker, and imaging markers of the disease that may bolster further research into the role of PACAP38 in migraine.

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Glossary

AD = axial diffusivity; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FMRIB** = Oxford Centre for Functional Magnetic Resonance Imaging of the Brain; **FSL** = FMRIB's Software Library; **MD** = mean diffusivity; **PACAP38** = pituitary adenylate cyclase-activating peptide 38; **PACAP38-LI** = pituitary adenylate cyclase-activating peptide 38-like immunoreactivity; **RD** = radial diffusivity.

Pituitary adenylate cyclase-activating peptide 38 (PACAP38) is a neuropeptide of growing importance in migraine literature. There are consistent reports of its migraine-inducing properties,[1,2] and its blood levels correspond with headache attacks, with decreased blood levels in the interictal term.[3] The exact nature of its connection to migraine, however, remains unclear. Research points to the involvement of PACAP38 in the activation of the trigeminovascular system,[4] and it has been affiliated with headache-related photophobia as well.[5]

Alterations of brain function and structure in migraine were identified with various MRI modalities. Magnetic resonance spectroscopy studies demonstrated neurochemical differences mainly in the cingulate and occipital cortices in patients with migraine.[6,7] Functional MRI studies found altered activation in regions related to pain processing, and the activity of resting-state networks was also shown to be altered in migraine.[8] Several diffusion tensor imaging (DTI) studies found microstructural abnormalities of the white matter in patients with migraine in pathways related to pain sensation[9] and visual processing.[10] Since PACAP38 turns up as a functional molecule in these systems,[11,12] the question arises whether the peptide's assumed role in migraine pathophysiology is linked to alterations of the white matter microstructure. A recent study by Yilmaz et al.[13] revealed increased ictal levels of S100B (a marker of glial damage) and neuron-specific enolase (a marker of neuronal damage) in migraineurs without aura. Furthermore, infusion of PACAP38 in migraineurs changed the plasma concentrations of S100B.[14] Combined with decreased interictal levels of PACAP38, these results led us to the hypothesis that PACAP38 may induce degenerative changes in migraineurs that might be detectable with DTI. Alternatively, PACAP38 also exerts neurotrophic and neuroprotective effects,[15,16] and these effects might also be detected by diffusion MRI.

Serum levels of PACAP38 seem to approximately represent intracerebral PACAP38 metabolism in human studies since PACAP38 passes through the blood-brain barrier by way of a saturable transport mechanism,[17] and there are also reports of increased blood-brain barrier permeability in migraine.[18] Since decreased interictal PACAP38 levels could hypothetically be a product of altered PACAP38 metabolism, which might coexist with microstructural changes, we hypothesized that interindividual variation of subnormal interictal PACAP38 levels in patients with migraine might correlate with microstructural characteristics. In this exploratory study, we investigated this correlation in patients with migraine, as measured by DTI.[19]

Methods

Participants

We recruited 26 patients with migraine from outpatients of the Headache Outpatient Clinic at the Department of Neurology. Patients were diagnosed according to the International Headache Society criteria.[20] Participants were screened for depression using the Hamilton Depression Scale,[21] and those with a test result of >8 points were excluded. Apart from migraine, participants did not have any neuropsychiatric illnesses. Of 26 patients, 8 received prophylactic treatment for migraine (2 topiramate, 6 iprazochrome).

Standard protocol approvals, registrations, and patient consents

The study was approved by the local ethics committee (87/2009), and written consent was provided by all participants.

Acquisition of MRI data

MRI scans took place in the interictal period, at least 1 week after the last migraine attack, using a 1.5T GE Signa Excite HDxt MRI Scanner (GE Healthcare, Milwaukee, WI). We obtained 3-dimensional fast spoiled gradient echo images (echo time = 4.1 milliseconds [ms]; repetition time = 10.276 ms; matrix: 256 × 256; field of view: 25 × 25 cm; flip angle: 15°; in-plane resolution: 1 × 1 mm; slice thickness: 1 mm) and 60 directional diffusion-weighted images with 6 non-diffusion-weighted reference volumes (echo time = 93.8 ms; repetition time = 16 ms; matrix: 96 × 96; field of view: 23 × 23 cm; flip angle: 90°; in-plane resolution: 2.4 × 2.4 mm; slice thickness: 2.4 mm; b = 1,000 s/mm^2; number of excitations = 2; array spatial sensitivity encoding technique factor = 2) for all participants, using similar parameters as published in our recent study.[22]

PACAP38-like immunoreactivity measurements

Blood samples were drawn interictally from the cubital vein just before MRI scans, while patients maintained a sitting position. The samples were collected in cooled glass tubes, which contained 12 mg of EDTA and aprotinin, a protease inhibitor (Trasylol 1,200 IU; Bayer Pharmaceuticals Corp., West Haven, CT). We kept the tubes at 4°C before centrifugation and stored them at −80°C afterward pending

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PACAP38-like immunoreactivity (PACAP38-LI) measurement with a specific and sensitive radioimmunoassay method published earlier.[3]

The PACAP38 antiserum "88111-3" was raised against synthetic peptides bound to bovine thyroglobulin or bovine serum albumin in rabbits. The tracers were labeled with mono-^{125}I and prepared in our laboratory. As standards, we used synthetic peptides in concentrations of 0 to 1,000 fmol/mL. We prepared the assay in 1 mL of 0.05 M (pH = 7.4) phosphate buffer that contained 0.1 M sodium chloride, 0.25% (w/v) bovine serum albumin, and 0.05% (wt/vol) sodium azide.

Following centrifugation at 2,000 rpm, 4°C, 10 minutes, precipitation with absolute alcohol took place and after another centrifugation at 2,000 rpm, 4°C for 10 minutes, we dried the samples under nitrogen flow and resuspended them in 300 μL of assay buffer. Afterward, we measured the antiserum (100 mL, diluted 1:10,000), the tracer (100 mL, 5,000 cpm/tube), and the standard/unknown samples (100 mL) into polypropylene tubes along with the assay buffer.

Table Clinical and demographic data of the patients

Patient	Age, y	Sex	Migraine type	Disease duration, y	Attack frequency, attacks/y	Allodynia score	VAS	Headache side
1	33	F	MwoA	15	36	1	7	A
2	34	F	MwoA	3	52	8	8	R
3	54	F	MwoA	20	12	0	10	R
4	30	F	MwA	16	18	2	6	L
5	29	F	MwoA	18	36	2	8	L
6	38	F	MwoA	30	60	6	9	A
7	53	F	MwoA	24	12	10	5	L
8	23	F	MwA	8	72	2	7	R
9	21	F	MwoA	1	12	0	10	L
10	27	F	MwoA	3	52	9	7	L
11	38	F	MwoA	13	120	0	9	A
12	24	M	MwA	7	1	0	7	R
13	44	F	MwoA	32	24	2	9	A
14	37	F	MwA	9	3	2	7	A
15	37	F	MwoA	27	36	0	9	A
16	33	F	MwoA	15	48	0	9	A
17	28	F	MwoA	5	120	4	7	A
18	46	F	MwoA	31	30	0	8	A
19	29	F	MwA	10	6	2	8	A
20	35	F	MwA	18	53	4	8	L
21	28	F	MwoA	4	60	3	9	A
22	25	F	MwoA	7	36	8	8	L
23	47	F	MwoA	11	182	6	8	R
24	38	F	MwoA	12	30	2	10	A
25	24	M	MwA	11	8	0	6	A
26	42	F	MwA	31	36	0	7	R
Mean ± SD	34 ± 9.05			14.65 ± 9.54	44.42 ± 41.59	Median 2, mode 0	Median 8, mode 7	

Abbreviations: A = alternating; MwA = migraine with aura; MwoA = migraine without aura; VAS = visual analog scale.

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Following incubation for 48 to 72 hours at 4°C, we separated peptides bound by antibodies from free ones by way of adding 100 mL of separating solution (containing 10 g charcoal, 1 g dextran, 0.5 g fat-free milk powder dissolved in 100 mL of distilled water). After another centrifugation at 3,000 rpm, 4°C for 15 minutes, we carefully decanted the tubes' contents and measured the radioactivity of the precipitates in a gamma counter (NZ310; Gamma, Budapest, Hungary). Finally, we read the concentration values of PACAP38 in the unknown samples from the calibration curves.

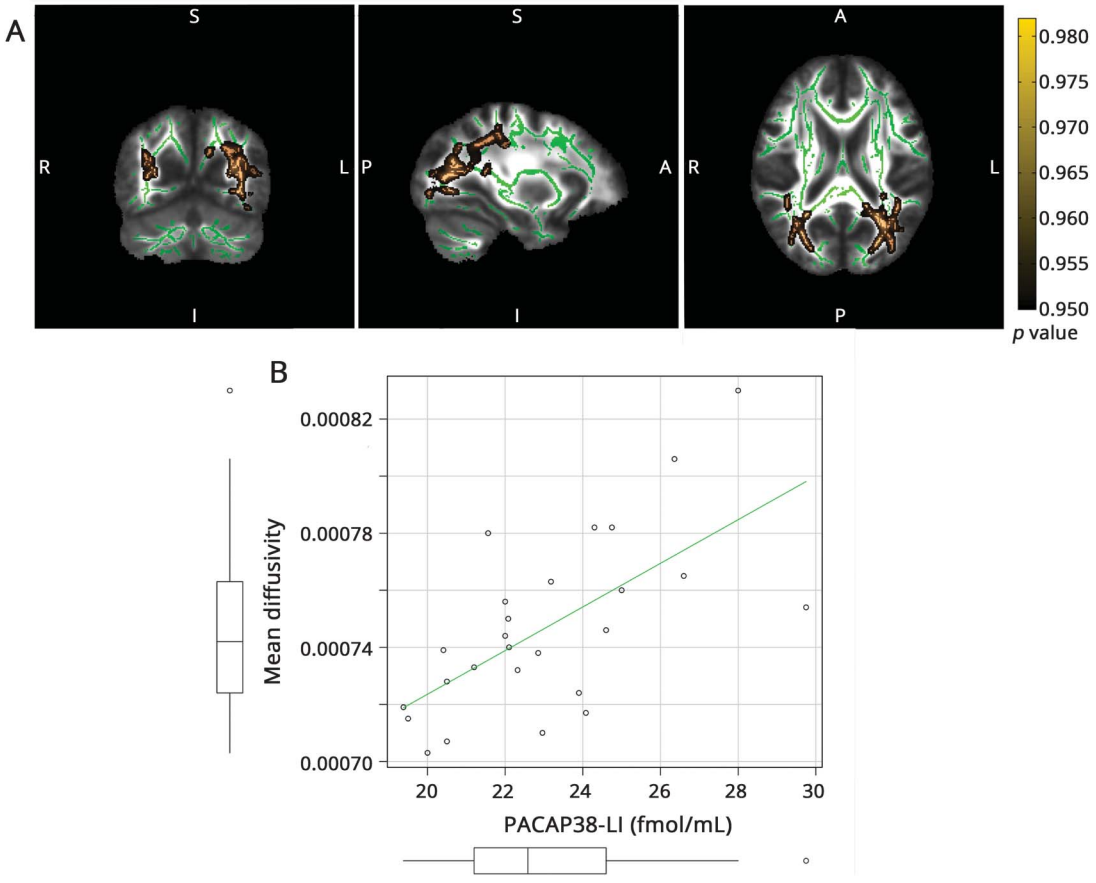
MRI analysis

We performed analysis of MRI data using FMRIB's Software Library (FSL version 5.0, fmrib.ox.ac.uk/fsl).[23] The obtained diffusion-weighted images underwent correction for eddy currents and movement artifacts using a 12 degrees of freedom affine linear registration to the first reference volume without diffusion weighting.[24] Diffusion tensors were fitted in each voxel of the motion- and eddy-corrected diffusion data using the algorithm included in FSL's FDT (FMRIB's Diffusion Toolbox).[25] We calculated fractional anisotropy (FA), mean diffusivity (MD), and diffusivity parallel (λ1, axial diffusivity [AD]) and perpendicular ([λ2 + λ3]/2, radial diffusivity [RD]) to the main direction of diffusion in the whole brain.

We performed statistical analysis of the FA data in each voxel via tract-based spatial statistics.[26] All participants' FA data were allineated into standard space using nonlinear registration as implemented in FSL's FNIRT (FMRIB's nonlinear image registration tool),[27] which uses a b-spline representation of the warp field utilized during registration.[28] Next, a mean FA image was calculated and then thresholded at 0.2 to produce a mean FA skeleton representing the centers of white matter tracts shared by the group. Each participant's aligned FA data were then projected onto the mean FA skeleton, and the skeletonized images were fed into voxelwise cross-subject statistics.

We calculated linear correlation between diffusion measures (FA, MD, AD, RD) and PACAP38-LI in each voxel using a standard general linear model design with permutation-based cluster analysis as realized in FSL,[29] with age and sex as

Figure 1 Correlation of PACAP38-LI and mean diffusivity



(A) The skeleton is overlaid in green on the mean fractional anisotropy image. Significant correlations are depicted in copper (maximum *p* value MNI coordinates: x = 125, y = 69, z = 75). Clusters are thickened for better visualization. The color bar represents 1 − *p* values corrected for multiple comparisons. (B) Scatterplot PACAP38-LI is plotted against average mean diffusivity under the significant voxels. The boxplots stand for mean, 95% confidence interval, and range. Outliers are depicted with open circles. MNI = Montreal Neurological Institute; PACAP38-LI = pituitary adenylate cyclase-activating peptide 38-like immunoreactivity.

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nuisance regressors in the model. Although no clinical variables correlated with interictal PACAP38-LI in the studied patients, we also tested another model with disease duration included as an additional nuisance regressor, as it was previously shown to correlate with interictal PACAP38-LI in a larger sample of patients.[3] Clusters were formed using the threshold-free cluster enhancement method,[30] and correction for multiple comparisons was performed using FSL's randomise tool[31] at a threshold of $p < 0.05$.

Data availability

Anonymized data will be shared on request through personal correspondence after the approval of the local ethics committee.

Results

Demographic and clinical data of the patients

Twenty-six patients with migraine were recruited into the study, 8 of whom had migraine with aura. Aura symptoms were visual except for a male and a female patient who had additional somatosensory symptoms. The demographic and clinical data of the patients are summarized in the table. [T1]

Correlation of PACAP38-LI and white matter microstructure

Interictal plasma PACAP38-LI showed significant correlation MD ($p < 0.0179$, corrected for multiple comparisons) in the bilateral occipital white matter reaching into parietal and temporal white matter (figure 1). [F1]

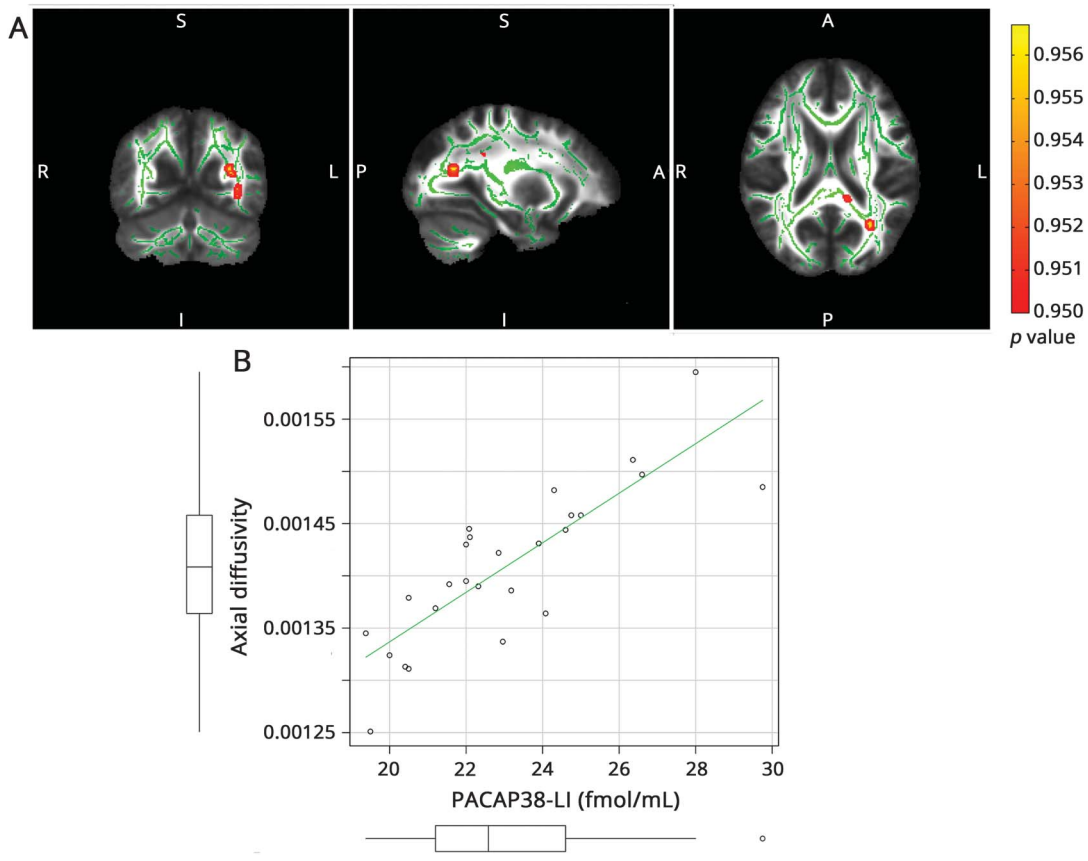
The correlation with AD was significant ($p < 0.0432$, corrected for multiple comparisons) in the left optic radiation and left posterior corpus callosum (figure 2). [F2]

RD correlated with interictal PACAP38-LI ($p < 0.0418$, corrected for multiple comparisons) in the left optic radiation and parietal white matter (figure 3). FA did not show any significant correlation with interictal PACAP38-LI. [F3]

Correlation of PACAP38-LI and diffusion measures with disease duration as nuisance regressor

With age, sex, and disease duration as nuisance regressors, interictal PACAP38-LI showed significant correlation with MD and AD in the left thalamus ($p < 0.01$, corrected for

Figure 2 Correlation of PACAP38-LI and axial diffusivity



(A) The skeleton is overlaid in green on the mean fractional anisotropy image. Significant correlations are depicted in red-yellow (maximum *p* value MNI coordinates: x = 125, y = 69, z = 75). Clusters are thickened for better visualization. The color bar represents 1 − *p* values corrected for multiple comparisons. (B) Scatterplot PACAP38-LI is plotted against the average axial diffusivity under the significant voxels. The boxplots stand for mean, 95% confidence interval, and range. Outliers are depicted with open circles. MNI = Montreal Neurological Institute; PACAP38-LI = pituitary adenylate cyclase-activating peptide 38-like immunoreactivity.

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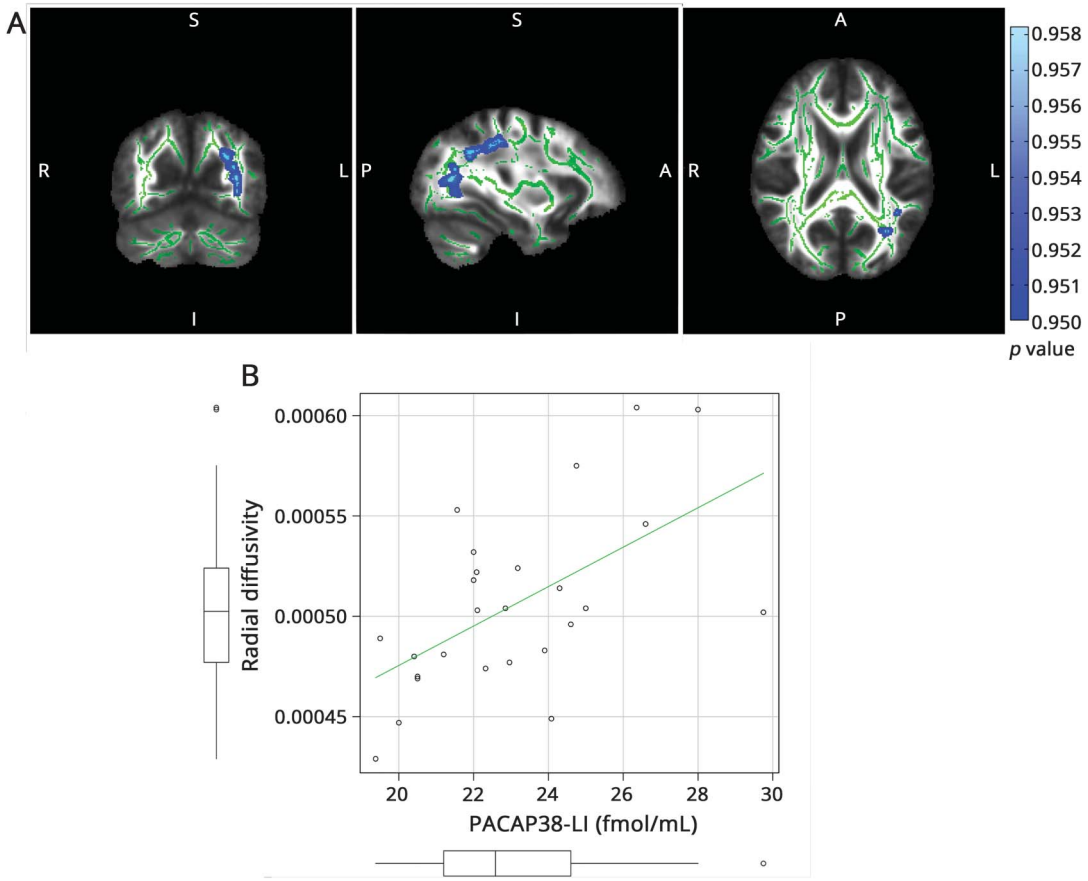
Figure 3 Correlation of PACAP38-LI and perpendicular diffusivity



(A) The skeleton is overlaid in green on the mean fractional anisotropy image. Significant correlations are depicted in blue/light blue (maximum *p* value MNI coordinates: x = 115, y = 64, z = 102). Clusters are thickened for better visualization. The color bar represents 1 − *p* values corrected for multiple comparisons. (B) Scatterplot PACAP38-LI is plotted against the average perpendicular diffusivity under the significant voxels. The boxplots stand for mean, 95% confidence interval, and range. Outliers are depicted with open circles. MNI = Montreal Neurological Institute; PACAP38-LI = pituitary adenylate cyclase-activating peptide 38-like immunoreactivity.

[F4] multiple comparisons) (figure 4). We found no significant correlation with FA and RD.

Discussion

Herein, we report significant correlation between diffusion parameters of the white matter and interictal plasma PACAP38-LI in patients with migraine in the occipital white matter. Similar to our former results,[3] the interictal PACAP38-LI was lower than in normal healthy controls.

Interpretation of diffusion measures in terms of microstructural characteristics is a much-debated area complicated by the fact that microstructural properties are probed in a few millimeter large elements of the space. However, it is generally accepted that lower FA or higher MD corresponds to reduced white matter integrity. AD and RD are suggested to correlate with the number of axons and the integrity of the myelin, respectively.[32,33] As such, our results could be interpreted as follows: abnormally lower plasma PACAP38 levels in the interictal phase are accompanied by decreased values of MD, AD, and RD representing higher axonal density and/or myelination, or generally more compact white matter in the optic radiation, corpus callosum, and temporoparietal regions. The absence of correlation with FA may be attributable to the fact that FA is a measure that combines AD and RD; if there is a similar change in both AD and RD, FA would change only if the magnitude of change is different in the 2 perpendicular directions.

Considering that interictal hyperexcitability of the cortex in migraineurs has been demonstrated before,[8,34] and this increased baseline activity might also reveal to be maladaptive plasticity leading to more compact white matter, our results could be an indication of such maladaptive remodeling in response to migraine symptoms that is in connection with PACAPergic signaling. In particular, a functional MRI study of PACAP38-induced migraine-like attacks found increased connectivity of the left visual cortex in the default-mode network.[35] This increased connectivity and presumable activity could also lead to increased structural connections.

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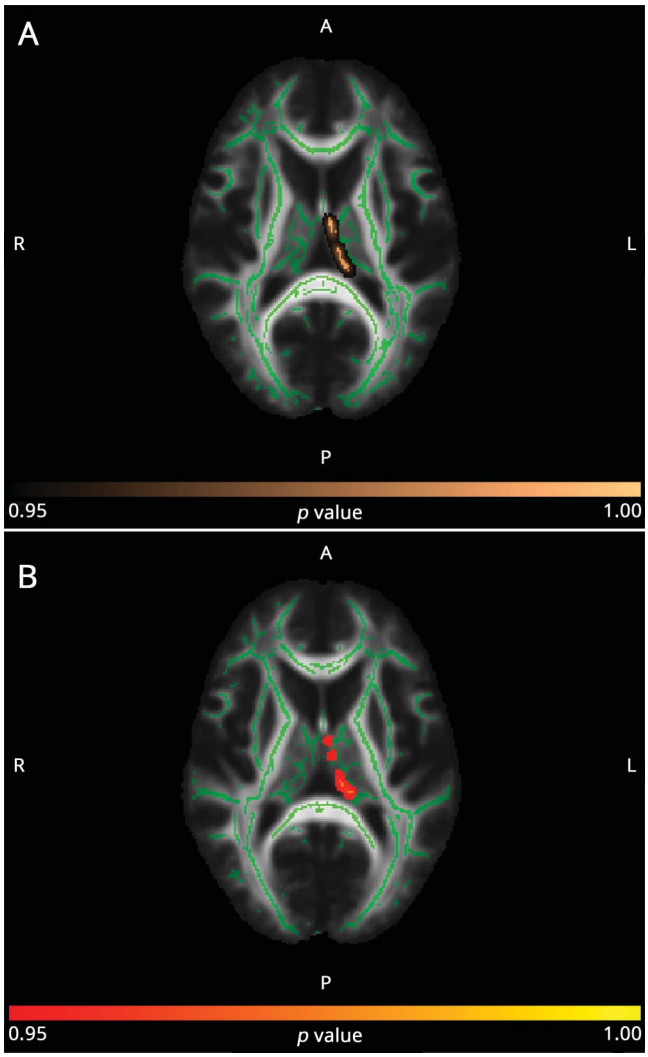
Figure 4 Correlation of pituitary adenylate cyclase-activating peptide 38-like immunoreactivity and axial and mean diffusivity with disease duration as nuisance regressor



The skeleton is overlaid in green on the mean fractional anisotropy image. Significant correlations are depicted in red for axial diffusivity (A) and copper for mean diffusivity (B) (maximum *p* value MNI coordinates: mean diffusivity: x = 98, y = 101, z = 85; axial diffusivity: x = 102, y = 96, z = 82). Clusters are thickened for better visualization. The color bar represents 1 − *p* values corrected for multiple comparisons. MNI = Montreal Neurological Institute.

Of course, it might also be possible that the connection between PACAP38 and white matter integrity is purely coincidental and decreased interictal plasma PACAP38 levels reflect changes in PACAPergic signaling that contribute to disrupted neurochemical coupling in migraine, as demonstrated by magnetic resonance spectroscopy studies.[36] In the long term, these functional alterations may prove to be structural changes.

Longitudinal studies might help in understanding the exact nature of these connections. The location of correlating diffusion measurements suggests involvement of the visual system, many aspects of which are affected in migraine.[37] Photophobia is a prominent accompanying symptom present in a large percentage of migraineurs, and bright light is known to exacerbate migrainous headache. The phenomenon is thought to originate in part from intrinsically photosensitive retinal ganglionic cells[38] that express PACAP38 to be used as a cotransmitter in retinohypothalamic projections.[12,39,40] Neurons of the suprachiasmatic nucleus on the receiving end of these pathways connect to and modulate light-sensitive neurons in the trigeminal nucleus caudalis,[41] an area that also contains PACAP38-expressing neurons,[42] thus providing possible linkage between the visual and trigeminovascular system. Intrinsically photosensitive retinal ganglionic cells also show direct connections to thalamic pain centers in rats[43] and have been thought to be part of a photophobia pathway that involves direct stimulation of trigeminal afferents in the eye without interposition of the optic nerve.[44,45]

Other animal studies link PACAP38 to behavioral aspects of photophobia: PACAP-deficient mice, after nitroglycerol-induced activation of the trigeminovascular system, exhibit light avoidance to a lesser degree than their wild-type counterparts.[46] In light of the above, it is possible that reduced interictal PACAP38 levels reflect changes in photophobia-associated signaling that co-occur with alterations of fiber integrity in the optic tract, which would also be corroborated by the finding that PACAP38 uptake peaks in the occipital cortices after intranasal administration in mice.[17]

The correlation between the white matter microstructural measures and the PACAP38 immunoreactivity was somewhat lateralized. Formerly, we showed that the diffusion characteristics of subcortical structures are asymmetric,[47] which might be present in major white matter tracts as well.[48] Although they did not reach significance when corrected for multiple comparisons, there are voxels in the contralateral white matter that mirror significant results at a more liberal statistical threshold.

The change in the pattern of correlating diffusion measurements with the inclusion of disease duration as a nuisance regressor suggests that altered PACAP38 metabolism and its effect might develop as a function of disease progression, though it is unclear whether this is due to disease pathology or accumulating effects of allostatic load. In another study, we found that longer disease duration corresponds with decreased values of AD in the left parietooccipital regions in migraine patients with aura,[22] which co-occur with PACAP38-related alterations in the current study. Considering that decreased PACAP38 levels correlate with diffusion measures of the left thalamus irrespective of disease duration, we would suggest that PACAP38 might have a few different roles in the development of white matter alterations, which should be addressed in further studies.

One limitation of our study is the heterogeneity of the patient population because of the inclusion of migraine

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patients both with and without aura. Based on our recent results, there are microstructural differences in the 2 groups that would necessitate regarding them as separate entities.[22] Hence, we repeated the analysis separately for patients with and without aura. Since group sizes are considerably smaller, no significant correlation was found in either group with interictal PACAP38-LI. However, looking at the uncorrected results, we can identify similar patterns of correlation in both groups (data available from Dryad [Material]: doi.org/10.5061/dryad.g58811v), which would indicate no major differences in terms of correlating PACAP38-LI and diffusion measures. Still, studies deploying greater sample sizes are needed to assess differences between migraine patients with and without aura.

Also, since PACAPergic signaling seems to be altered in migraine, we decided to focus our study on the interindividual variation of PACAP38-LI in patients with migraine. However, information about the relationship between PACAP38-LI and white matter diffusion measures in healthy controls is rare in the literature. Controlled studies are needed to assess possible differences in the relationship between PACAP38 levels and microstructural characteristics in healthy controls and migraineurs.

While various MRI measures are useful biomarkers of migraine, direct connection between the disease and MRI features is still to be established. Providing connection between a pathobiologically important neurochemical biomarker of the disease and MRI alterations found in migraine emphasizes the value of both markers and opens up new directions of investigations.

Author contributions

Dániel Veréb: study concept and design, data acquisition, analysis and interpretation, writing the manuscript. Nikoletta Szabó: study concept and design, data acquisition, analysis and interpretation, drafting the manuscript. Bernadett Tuka: data acquisition, interpretation, drafting the manuscript. János Tajti: contribution to study design, study supervision, revising the manuscript for important intellectual content. András Király: data acquisition and analysis, revising the manuscript for important intellectual content. Péter Faragó: data acquisition and analysis, revising the manuscript for important intellectual content. Krisztián Kocsis: data acquisition and analysis, revising the manuscript for important intellectual content. Eszter Tóth: data acquisition and analysis, revising the manuscript for important intellectual content. Bálint Kincses: data analysis, revising the manuscript for important intellectual content. Teréz Bagoly: data acquisition. Zsuzsanna Helyes: contribution to study design, data acquisition, revising the manuscript for important intellectual content. László Vécsei: contribution to study design, study supervision, revising the manuscript for important intellectual content. Zsigmond Tamás Kincses: study concept and design, study supervision, drafting the manuscript.

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Disclosure

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