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Microstructural Evidence of Neuroinflammation for Psychological Symptoms and Pain in Patients With Fibromyalgia

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ABSTRACT. ***Objective.*** In patients with fibromyalgia (FM), the brain shows altered structure and functional connectivity, but the mechanisms underlying these changes remain unclear. This study investigated the associated changes in brain microstructures and neuroinflammation of patients with FM.

Methods. We recruited 14 patients with FM and 14 healthy controls (HCs). Visual analog scale (VAS), Beck Anxiety Inventory (BAI), and Beck Depression Inventory-II (BDI-II) were used for assessing their pain, anxiety, and depression levels, respectively. Diffusion kurtosis imaging (DKI) was used to visualize microstructural alterations associated with neuroinflammation in specific brain regions. The biomarkers for neuron damage, including serum tau and amyloid β protein fragment 1-42 (Aβ1-42) levels, were assessed. Spearman correlation of DKI parameters with VAS, BAI, and BDI-II scores as well as tau and Aβ1-42 levels were assessed.

Results. The patients with FM had significantly higher levels of Aβ1-42 levels than HCs. Compared with HCs, the patients with FM showed significantly lower DKI parameters in the bilateral dorsolateral prefrontal cortex and orbitofrontal cortex. Patients with FM showed a significant correlation between the axial kurtosis values of the amygdala and VAS scores (left: $\rho = -0.60$, $P = 0.02$; right: $\rho = -7.04$, $P = 0.005$).

Conclusion. To the best of our knowledge, this is the first study to use DKI to examine the brains of patients with FM. We noted significant DKI changes associated with neuroinflammation at specific areas in patients with FM. Our results provide valuable information on brain neuroinflammation and pathophysiological changes in patients with FM.

Key Indexing Terms: anxiety, depression, diffusion kurtosis imaging, fibromyalgia, neuroinflammation, pain

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Fibromyalgia (FM) is a relatively common chronic pain disorder. The pathomechanism of FM may involve pain dysregulation in the central nervous system (CNS).[1] The pain transmission and modulation pathways involving specific areas such as the mesolimbic system, anterior cingulate cortex (ACC), and insula are altered in patients with FM.[2] Functional magnetic resonance imaging (fMRI) highlighted the presence of abnormal pain and other sensory processing in patients with FM.[3] Further, patients with FM exhibit structural changes in the brain, such as regional gray and white matter loss.[4] Diffuse tensor imaging (DTI), which can provide information on brain microstructure integrity, is used to evaluate neural tracts.[5] Significant decreases in fractional anisotropy in the bilateral thalami, the thalamocortical tracts, and insular regions have been reported in patients with FM. In these patients, pain intensity scores were correlated with DTI parameters in the right superior frontal gyrus.[4] The altered regional brain microstructure is associated with symptom profiles in patients with FM.

The underlying mechanisms of structural changes in patients with FM remain unclear. Accumulating evidence shows that abnormal glial cell activation and neuroinflammation are key factors associated with chronic pain.[6] Substance P, glutamate,

nerve growth factor, and brain-derived neurotrophic factor levels are higher in the cerebrospinal fluid of patients with FM.[7] These substances can activate microglia and astrocytes, leading to the release of proinflammatory cytokines such as interleukin (IL)-1β and IL-8. IL-8 is positively associated with increased pain intensity in patients with FM.[7]

Diffusion kurtosis imaging (DKI) estimates the kurtosis of water diffusion probability distribution function. The orientation of water diffusion is affected by changes in cellular membranes, intracellular organelles, and myelinated axons in the brain.[8] The DKI method can provide detailed information about microstructural and microenvironmental changes in the brain.[9] Compared with DTI, DKI can more accurately detect microstructural alterations in the brain of patients with major depression.[10] A mouse model study showing neuroinflammation was associated with a significant decrease in regional DKI parameters such as mean kurtosis (MK), radial kurtosis (RK), and axial kurtosis (AK).[11] An autoimmune encephalomyelitis study used DKI parameters to investigate neural damage as indicated by inflammatory lesions, demyelination, and axonal damage and was supported using DKI-derived biomarkers to detect neuroinflammation.[12]

No data regarding the DKI features in the brain of patients with FM are available. In the present study, we used DKI to investigate the microstructural changes for detecting focal neuroinflammation of the brain in patients with FM. Further, we examined the correlations between DKI parameters, blood biomarkers of neurodegeneration and neuroinflammation, psychological symptoms, and pain in patients with FM. Our results can provide valuable information on the role of neuroinflammation in patients with FM.

METHODS

Participants. This study included 14 female patients with FM (mean age 50.6 yrs) and 14 female healthy controls (HCs; mean age 56.9 yrs). Each participant provided her informed consent. The Joint Institutional Review Board of the Taipei Medical University (N201812078) approved this study. The FM group consisted of patients from Taipei Medical University Hospital who met the American College of Rheumatology 2016 criteria for FM. We excluded patients who (1) had a malignancy; (2) had an active or chronic infection; (3) had dementia, a CNS disorder, or head trauma; (4) had an endocrine disorder; (5) had a major autoimmune disorder such as systemic lupus erythematosus or rheumatoid arthritis; and (6) were pregnant. The control group comprised healthy people without a current history of known disease and drug use. The patients were requested to stop taking medications, except acetaminophen, for at least 2 weeks before clinical evaluation and blood analysis. For blood analysis, 10 mL of blood was drawn from a forearm vein after the participants woke up in the morning, before they had any meals.

Questionnaires. Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI) are 21-item self-reported questionnaires that assess depression and anxiety severity, respectively. Each item is rated from 0 (not severe at all) to 3 (very severe), with a maximum possible score of 63. The visual analog scale (VAS) of pain is used to evaluate the average pain level. This scale is a 10-cm ruler, with markings ranging from 0 (no pain) to 10 (the worst imaginable pain). We requested that patients mark points corresponding to the average pain level in the past week.

Immunomagnetic reduction assay for tau protein and amyloid β protein fragment 1-42. We used an immunomagnetic reduction assay (IMR) to measure blood tau protein (tau) and amyloid β protein fragment 1-42 (Aβ1-42) levels. IMR uses antibody-functionalized magnetic nanoparticles. The concentrations of detected molecules are calculated by the magnetic susceptibility associated with the interaction between the magnetic nanoparticles and molecules. A superconducting quantum interference device achieves ultra-high sensitivity for detecting extremely low concentrations of Aβ1-42 and tau. The study has revealed the high consistency in IMR analysis.[13] IMR can precisely assay the Aβ1-42 or tau protein concentrations at several tens of pg/mL compared with ELISA.[13] The magnetic reagents MF-AB2-0060 and MF-TAU-0060 were used to assay the serum biomarkers Aβ1-42 and tau on the Xacpro-S detector (MagQu).

MRI data acquisition and DKI data analysis. All brain images were acquired on a 3T MRI system (MAGNETOM Prisma; Siemens) equipped with a 20-channel head coil. To obtain an anatomical reference, we performed high-resolution T1-weighted imaging using a 3D magnetization-prepared rapid gradient echo sequence: repetition time (TR)/echo time (TE) 2000 ms/2.3 ms, flip angle 8°, field of view (FOV) 240 × 240 mm, acquisition matrix 256 × 256, all of which resulted in an isotropic spatial resolution of 1 mm^3. A whole-brain diffusion-weighted sequence was applied with the following parameters: TR/TE 5700 ms/84 ms, slice thickness 2.70 mm, and acquisition matrix 82 × 82. Diffusion weighting with 2 b factors 1000 and 2000 s/mm^2 was performed along 64 directions, complemented by 1 scan without diffusion gradient.

FMRIB Software Library (FSL; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) was used in the preprocessing of MRI images, which included skull stripping, motion correction, and DKI that was registered to the first acquired b0 image on all diffusion-weighted images for motion correction. Local principal component analysis and correction were conducted before image reconstruction. Targeted regions of interest (ROIs) were selected by using the Talairach space, and the preprocessed b0 image was registered with the standard space by FSL flirt command in the affine transformation method. DKI data were analyzed using an in-house program with MATLAB (MATLAB 2021a; The MathWorks Inc.). We calculated 3 DKI parameters, including MK, AK, and RK, in each targeted ROI that contributes to the psychological domain of pain, including the insula, amygdala, hippocampus, dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), and thalamus (Figure 1A).

Statistical analysis. DKI parameters were analyzed using the independent 2-tailed *t* test to compare the differences between the FM and control groups. Spearman ρ was calculated to investigate the correlation of DKI parameters with Aβ1-42 levels and anxiety scores. The significance level was set at $P < 0.05$. We applied the Bonferroni correction for multiple comparisons with the false discovery rate (FDR) set at $P < 0.05$ level. We used the IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp) to perform data analyses.

RESULTS

The patients with FM had significantly higher mean (SD) scores on BAI (13.4 [8.9] vs 4.2 [3.6], $P = 0.001$) and BDI-II (11.4 [8.6] vs 3.4 [5.9], $P = 0.003$) compared with HCs. Tau levels showed no significant difference between the 2 groups. Aβ1-42 levels were significantly higher in the patients (17.05 [0.45] pg/mL) than in HCs (16.52 [0.39] pg/mL, $P = 0.003$; Table 1). MK and RK values in the bilateral DLPFC and bilateral OFC, and the AK value in the left DLPFC were significantly lower in the patients with FM than in HCs (Figure 1C). Spearman correlations of DKI parameters with mean Aβ1-42 levels and BAI and BDI-II scores with the Bonferroni correction for correcting multiple comparisons with the FDR were examined. The results indicated negative correlations between mean Aβ1-42 and MK, AK, and RK in the left DLPFC of the

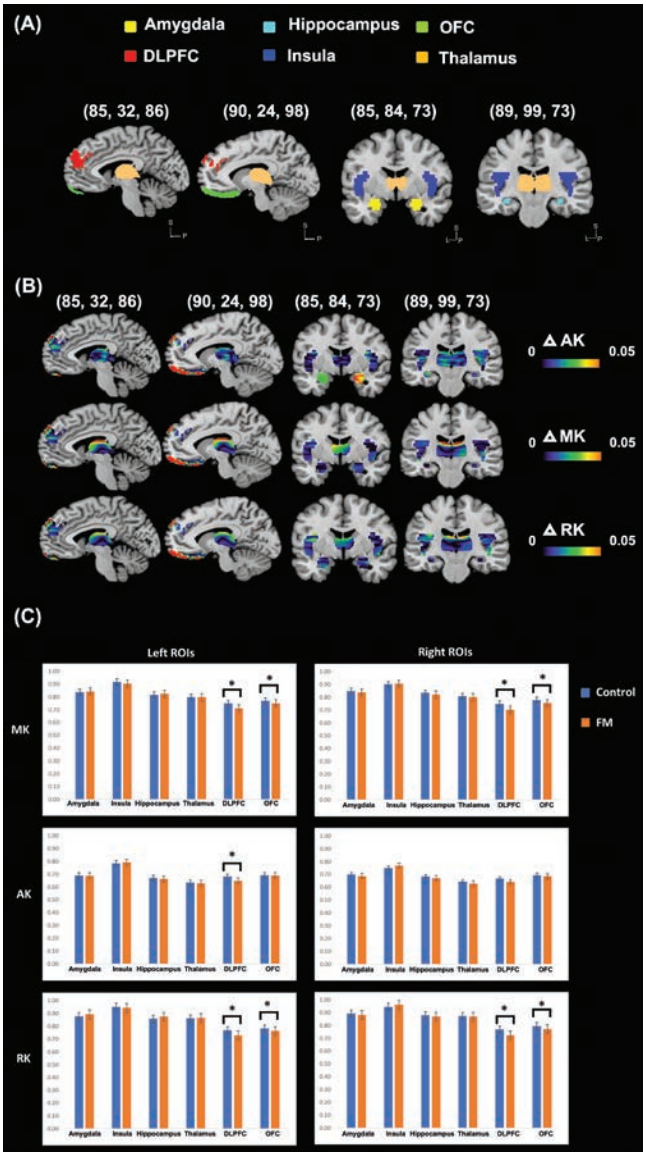

Figure 1. (A) Six pairs of targeted regions of interest (ROIs) with the coordinates in the sagittal and the coronal view. Colors are used to label the ROIs. (B) Differences in the axial kurtosis (AK), mean kurtosis (MK), and radial kurtosis (RK) values of the targeted ROIs between the HC and FM groups. ΔAK calculated as [Control]_AK − [FM]_AK, where [Control]_AK and [FM]_AK are the average AK values in the control and FM groups, respectively. Similar formulas were applied to obtain ΔMK and ΔRK. (C) Bilateral dorsolateral prefrontal cortex (DLPFC) and bilateral orbitofrontal cortex (OFC) showing significantly lower MK values in the FM group than in the HCs. The left DLPFC of the FM group showed a significant lower AK value than did that of the HCs. Moreover, bilateral DLPFC and bilateral OFC showed a significantly lower RK value in the FM group than in HCs. FM: fibromyalgia; HC: healthy control.

patients with FM. The mean Aβ1-42 levels in HCs were significantly and positively correlated with MK and RK values in their left insula and MK and RK values in their bilateral OFC (Table 2). No significant correlation was noted between BAI scores and DKI parameters in the patients with FM. The VAS scores of the patients with FM were significantly correlated with AK values in their left amygdalae (left: $\rho = -0.60$, $P = 0.02$; right: $\rho = -7.04$, $P = 0.005$).

DISCUSSION

We found that the patients with FM showed significant decreases in the DKI parameters of the left DLPFC. A positron emission

Table 1. Participant demographic characteristics and clinical profiles.

	HCs, n = 14	FM, n = 14	*P*
Age, yrs	50.6 (7.6)	56.9 (7.2)	0.03
BMI, kg/m^2	25.6 (4.8)	23.5 (4.5)	0.25
Clinical profiles			
BAI score	4.2 (3.6)	13.4 (8.9)	0.001
BDI-II score	3.4 (5.9)	11.4 (8.6)	0.003
Tau level, pg/mL	23.54 (4.01)	23.23 (3.68)	0.84
Aβ1-42 level, pg/mL	16.52 (0.39)	17.05 (0.45)	0.003
VAS	–	5.4 (2.2)	–

Values are expressed as mean (SD) unless otherwise indicated. Aβ1-42: amyloid β protein fragment 1-42; BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory-II; FM: fibromyalgia; HC: healthy control; VAS: visual analog scale.

tomography (PET)-based study found an increased level of a glial activation marker, the [^{11}C]-PBR28 signal, indicating neuroinflammation and specific microgliosis at the primary somatosensory cortex, primary motor cortex, DLPFC, superior parietal lobule, supramarginal gyrus, supplementary motor area, posterior cingulate cortex, and dorsomedial prefrontal cortex in patients with FM.[14] The decrease in DKI parameters of the DLPFC in our study is compatible with the results of the PET study.[14] We suggested that DKI could be an alternative imaging tool in examining the neuroinflammatory state of patients with FM. Neuroinflammation can result in axon damage or demyelination and secondary structural changes. While both PET and DKI may detect neuroinflammation in the brain, the 2 modalities reflect different mechanisms of inflammation. The PET-based imaging can visualize the specific area of gliocyte or astrocyte activation. In contrast, DKI is based on the diffuse ability of water, mainly associated with the focal microstructural derangement. Further study is needed on performing these 2 modalities simultaneously (PET/MRI) to explore the detailed pathomechanism of neuroinflammation.

To our knowledge, our study is the first to apply DKI in examining the microstructural changes involving neuroinflammation in patients with FM. In addition to the left DLPFC showing significant decreases in all 3 DKI parameters (MK, RK, and AK), we found significant decreases in some DKI parameters at other areas such as the right DLPFC bilateral OFC. The DLPFC and the OFC functionally contribute to pain inhibition and sensory integration,[15] which correspond to pain regulation. Further, different DKI parameters may reflect different types of information over time during neuroinflammation. An immunohistochemical study showed that an increased MK value is associated with increased astrogliosis.[16] Another study reported that microgliosis is associated with increases in MK and RK values during acute inflammatory demyelination; however, the MK

Table 2. Spearman ρ correlation coefficients between DKI indexes in targeted ROIs

ROI	DKI Index	FM, n = 14			HCs, n = 14		
		Aβ1-42	BAI	BDI-II	Aβ1-42	BAI	BDI-II
Left insula	MK	ρ = 0.20, *P* = 0.50	ρ = −0.23, *P* = 0.42	ρ = −0.24, *P* = 0.40	**ρ = −0.67, *P* = 0.01***	ρ = −0.08, *P* = 0.80	ρ = −0.10, *P* = 0.74
	AK	ρ = 0.13, *P* = 0.67	ρ = −0.06, *P* = 0.83	ρ = −0.007, *P* = 0.98	ρ = 0.25, *P* = 0.41	**ρ = 0.52, *P* = 0.049***	ρ = −0.47, *P* = 0.09
	RK	ρ = −0.13, *P* = 0.67	ρ = 0.04, *P* = 0.91	ρ = −0.17, *P* = 0.56	**ρ = −0.58, *P* = 0.04***	ρ = −0.13, *P* = 0.66	ρ = −0.38, *P* = 0.19
Left DLPFC	MK	**ρ = −0.65, *P* = 0.01***	ρ = 0.08, *P* = 0.80	ρ = 0.43, *P* = 0.13	ρ = 0.17, *P* = 0.58	ρ = 0.46, *P* = 0.10	ρ =− 0.01, *P* = 0.97
	AK	**ρ = −0.68, *P* = 0.008***	ρ = −0.14, *P* = 0.64	ρ = −0.16, *P* = 0.59	ρ = 0.18, *P* = 0.55	ρ = 0.45, *P* = 0.11	ρ = 0.07, *P* = 0.80
	RK	**ρ = −0.64, *P* = 0.01***	ρ = 0.14, *P* = 0.64	ρ = 0.53, *P* = 0.05	ρ = 0.14, *P* = 0.64	ρ = −0.48, *P* = 0.08	ρ = −0.05, *P* = 0.86
Left OFC	MK	ρ = −0.19, *P* = 0.51	ρ = 0.11, *P* = 0.71	ρ = 0.28, *P* = 0.34	**ρ = 0.59, *P* = 0.04***	ρ = 0.11, *P* = 0.72	ρ = 0.39, *P* = 0.17
	AK	ρ = −0.21, *P* = 0.44	ρ = −0.13, *P* = 0.64	ρ = 0.10, *P* = 0.73	**ρ = 0.64, *P* = 0.02***	ρ = −0.19, *P* = 0.51	ρ = −0.14, *P* = 0.63
	RK	ρ = −0.02, *P* = 0.98	ρ = 0.02, *P* = 0.94	ρ = 0.14, *P* = 0.62	ρ = 0.30, *P* = 0.32	ρ = 0.08, *P* = 0.79	ρ = 0.13, *P* = 0.67
Right OFC	MK	ρ = 0.007, *P* = 0.98	ρ = 0.06, *P* = 0.85	ρ = 0.37, *P* = 0.19	**ρ = 0.60, *P* = 0.03***	ρ = 0.10, *P* = 0.73	ρ = 0.16, *P* = 0.60
	AK	ρ = 0.15, *P* = 0.62	ρ = −0.01, *P* = 0.97	ρ = 0.38, *P* = 0.20	**ρ = 0.69, *P* = 0.009***	ρ = −0.25, *P* = 0.40	ρ = −0.27, *P* = 0.35
	RK	ρ = 0.002, *P* = 0.99	ρ = −0.03, *P* = 0.93	ρ = 0.27, *P* = 0.36	ρ = 0.06, *P* = 0.86	ρ = 0.08, *P* = 0.80	ρ = −0.03, *P* = 0.91

Corrected *P* values using Bonferroni correction for multiple testing (false discovery rate < 0.05). * Significant difference after Bonferroni correction for multiple testing ($P < 0.05$). AK: axial kurtosis; Aβ1-42: amyloid β protein fragment 1-42; BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory-II; DKI: diffusion kurtosis imaging; DLPFC: dorsolateral prefrontal cortex; FM: fibromyalgia; HC: healthy control; MK: mean kurtosis; OFC: orbitofrontal cortex; ROI: region of interest; RK: radial kurtosis.

value decreases during the demyelination recovery period after cuprizone-induced demyelination.[11]

A study used integrated PET/MRI to investigate the neuroinflammatory signatures in different chronic pain conditions including chronic low back pain (CLBP) and FM. An elevation of 18kDa translocator protein (TSPO) level, which was expressed by activated glial cells, was observed in the brain of patients with CLBP and FM. TSPO signal was elevated in the thalamus of CLBP patients in 2 independent cohorts, whereas TSPO signal elevations in patients with FM showed little involvement of the thalamus.[17] Consistently, we found that DKI parameters in the thalamus did not show significant changes, suggesting that neuroinflammation rarely affects the thalamus in FM. Another study compared the difference between the patients with FM and complex regional pain syndrome (CRPS) by measuring the distribution volume ratio of [^{11}C]-(R)-PK11195 PET, representing the neuroinflammation level in the brain.[18] Higher neuroinflammation levels were seen at the left pre- and postcentral gyri of patients with FM, whereas higher neuroinflammation levels were observed at the medulla, left insula, left thalamus, left superior temporal gyrus, bilateral putamen, and bilateral medial orbital gyri in patients with CRPS.[18] Compatible with those findings,[18] there was no significant decrease in DKI parameters at the insula in patients with FM in our study.

Tau and Aβ proteins are involved in the pathomechanism of neurological degeneration and can serve as biomarkers for neuron damage. Tau plays a prominent role in the stability of axonal microtubules, and tau pathology is associated with neuroinflammation. Depression and anxiety disorders are common in people with FM. The depression severity is associated with tau accumulation in specific brain regions, including the entorhinal cortex and inferior temporal area.[19] We previously showed that the serum levels of tau and Aβ1-42 significantly increased in patients with FM.[20] We hypothesize that patients with FM could have a higher burden of regional neuronal damage associated with neuroinflammation. The present study found that a lower MK value is associated with a significantly higher serum Aβ1-42 level. Aβ1-42 is associated with phosphatidylcholine and sphingomyelin synthesis. Aβ1-42 oligomers can inhibit myelin formation. Our data suggested that the increase in the Aβ1-42 level might be associated with regional impaired myelination and neuronal damage throughout neuroinflammation.

We found that the anxiety score and the AK value in the left insula were negatively correlated. An fMRI study suggested that the mesolimbic dopamine system regulates the pain inhibitory system in patients with CLBP.[19] However, under depression and anxiety, the dopamine response to painful stimuli is insufficient.[21] A PET study found neuroinflammatory markers and stress scores were correlated in the left medial and superior frontal and left amygdala.[18] The higher stress level was correlated with higher neuroinflammation states in patients with FM, suggesting that stress may trigger neuroinflammation in patients.[18] Neuroinflammation in the patient with a major depressive episode was examined by TSPO and showed a significant increase in the insula, PFC, and ACC compared to HCs.[22] Abnormal amygdala activation to pain-related fear linked to treatment outcomes of FM.[23] Microglia activation and proinflammatory cytokine production in the basolateral amygdala have been found to enhance presynaptic glutamate release associated with anxiety- and depression-like behaviors.[24] We speculate that neuroinflammation specifically influences the mesolimbic dopamine system in patients with FM, leading to the dysfunction of the pain inhibitory system and mood regulation.

Our study has some limitations. First, the sample size was small, and it comprised Chinese women alone. Second, the cause-and-effect relationship could not be established because this was a cross-sectional study. Third, we did not compare our findings to patients with other chronic pain disorders. Fourth, we investigated only the serum levels of tau and Aβ1-42 as neuroinflammation biomarkers. Investigations of other biomarkers of neuroinflammation may aid in delineating the neuroinflammation characteristics of patients with FM. Finally, the present study showed different mean ages of patients with FM and HCs (56.9 vs. 50.6 yrs). The DKI has been investigated in the age-related change in the prefrontal cortex. They found no significant correlations between the DKI parameters over the age range of 47 years to 62 years.[25] The age difference between the 2 groups might not affect our results significantly.

Patients with FM had significant alterations in the DKI parameters of the DLPFC and OFC compared with HCs. These findings support site-specific neuroinflammation associated with microstructural changes in patients with FM.

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