Cutaneous Allodynia and Its Risk Factors in Korean Patients with Migraine: A Survey of Two Tertiary Care Hospitals

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Aims: To measure the prevalence of cutaneous allodynia in Korean patients with migraine and to characterize the differential risks of migraine-associated factors and psychiatric disorders in its development. **Methods:** The study included consecutive patients with migraine who visited headache clinics at two tertiary care hospitals. Questionnaires including the 12-item Allodynia Symptom Checklist (ASC-12) and the Migraine Disability Assessment (MIDAS) were administered to the patients. The Mini International Neuropsychiatric Interview-Plus, Version 5.0.0 (MINI), was performed to diagnose current major depressive disorder (MDD) and current generalized anxiety disorder (GAD). To determine the predictive factors of cutaneous allodynia, a two-step logistic regression model was used. **Results:** A total of 332 patients were eligible for the study. Chronic migraine (CM) was present in 140 patients (42.2%). Current MDD and current GAD were identified in 73 (21.9%) and 59 patients (17.7%), respectively. Cutaneous allodynia was present in 48 patients (14.5%). Univariate analyses indicated that cutaneous allodynia was associated with female gender, CM, medication overuse headache, headache intensity, photophobia, phonophobia, MIDAS grade, current MDD, and current GAD. Multivariate analyses revealed that current MDD was the strongest risk factor for cutaneous allodynia (adjusted odds ratio [AOR] = 4.552; 95% confidence intervals [CI] = 2.300–9.007; *P* = .000), followed by CM (AOR = 3.666; 95% CI = 1.787–7.521; *P* = .000) and photophobia (AOR = 2.707; 95% CI = 1.340–5.469; *P* = .005). **Conclusion:** Korean patients with migraine have a low prevalence of cutaneous allodynia. Both depression and migraine-associated features are important factors in the occurrence of cutaneous allodynia. *J Oral Facial Pain Headache 2016;30:323–329. doi: 10.11607/ofph.1687*

Keywords: *allodynia, depression, frequency, migraine, risk factor*

Cutaneous allodynia is pain perceived in response to non-nociceptive stimuli.[1] Central sensitization in second-order neurons in the trigeminal brainstem subnucleus caudalis or in third-order neurons in the thalamus has been proposed to be a primary mechanism for its development.[2] Cutaneous allodynia is therapeutically important, as it provokes chronic migraine and high disability rates in patients with migraine[3,4] and is associated with failure of triptan therapy during a migraine attack.[5,6] Although cutaneous allodynia is not included as part of the diagnostic criteria for migraine, it is a commonly associated feature in Western studies, being observed in approximately 60% to 79% of patients with migraine.[2,3,7–9] However, its frequency has been reported to be lower in studies of Asian patients, ranging from 17% to 48%.[10,11]

Many risk factors for cutaneous allodynia have been reported, including obesity, early age of onset, attack frequency, and headache disability; cutaneous allodynia is also more common among women.[3,8,9] Some studies have reported that comorbid psychiatric disorders, including depression and anxiety, were primary contributing factors in patients with migraine.[7–9,11] Using a regression model, Kao et al found that anxiety was associated with cutaneous allodynia severity[11] and Louter et al revealed that comorbid depression and a higher frequency of migraine attacks were stronger predictors of cutaneous allodynia than migraine type (ie, with or without aura).[9] This could be because

both central sensitization and pain perception can be modulated via descending pathways by supraspinal processes involved in cognition, attention, and emotion.[12–15]

The aim of the present study was to measure cutaneous allodynia frequency in Korean patients with migraine and to characterize the differential risks of migraine-associated factors and psychiatric disorders in the development of cutaneous allodynia.

Materials and Methods

Subjects

This study included new patients with migraine who had attended the headache clinics at two tertiary care hospitals, Kyungpook National University Hospital (KNUH) and Ulsan University Hospital, since September of 2013. Patients were adolescents or adults between the ages of 15 and 75. All patients were newly diagnosed with migraine at the initial visit or were previous patients with migraine who had no active migraine or psychotropic medication use within the previous month. A diagnosis of migraine was assigned based on criteria from the International Classification of Headache Disorders, beta version (ICHD-3 beta).[16] Patients were excluded if they had any of the following conditions that prevented effective interview or questionnaire completion: illiteracy; mental retardation; serious medical, neurologic, or psychiatric disorders; and alcohol or drug abuse. Patients with a probable migraine, or who declined to participate in the interview, were also excluded.

Study Design

This cross-sectional study was conducted as part of a hospital-based research program that examined the impact of psychiatric disorders on migraine and was approved by the Institutional Review Board. Written informed consent was obtained from all participants and afterwards each patient was interviewed and their demographic and clinical data collected. The clinical data obtained included the following: concurrent medical disease, type of migraine (ie, with or without aura), migraine chronicity (either episodic migraine [EM] or chronic migraine [CM]), family history of migraine, medication overuse headache (MOH), age of disease onset, disease duration (in years), migraine attack frequency, headache intensity, accompanying symptoms (photophobia, phonophobia, and osmophobia), migraine-associated disability, and comorbid depression or anxiety. Attack frequency was defined as the number of migraine attacks within the preceding 3 months. Headache intensity was measured using a visual analog scale (VAS). The VAS was applied using two different scoring parameters: the VASmax and the VASnow; VASmax was defined as the maximal headache intensity experienced during the prior 3 months and VASnow represented the headache intensity on the day of psychiatric interviews. Photophobia, phonophobia, and osmophobia were defined as the respective hypersensitivity to light, sound, and certain odors during migraine attacks causing related avoidance of those stimuli or migraine symptom aggravation. Patients were asked whether they experienced photophobia, phonophobia, or osmophobia within the preceding year.

Cutaneous allodynia was assessed by questionnaire using the 12-item Allodynia Symptom Checklist (ASC-12), which defines patients with a cutoff score of > 2 as having cutaneous allodynia.[3] At the time of the present study, the ASC-12 had not been validated in Korean. Thus, the original English version was initially translated into Korean and the translated version was back-translated into English by a Korean-English teacher. Finally, the two versions were compared by a native English speaker, who verified that they were identical. Cronbach's α coefficient for the Korean version was 0.876, which indicates a good internal consistency. Family migraine history was defined as the presence of migraines in lineal ascendants or siblings. Migraine disability was measured using the Migraine Disability Assessment Scale (MIDAS).[17] The overall extent of disability was defined as follows: grade I, little or no disability (a score of 0–5); grade II, mild disability (a score of 6–10); grade III, moderate disability (a score of 11–20); and grade IV, severe disability (a score of 21 or more). Patients rated with disability grades I and II were compared with those rated at grades III and IV. Comorbid depression and anxiety were measured by psychiatric interview.

Psychiatric Interviews

All participants were interviewed by a neuropsychologist within 2 weeks after their first visit to determine whether they currently had a major depressive disorder (MDD) or generalized anxiety disorder (GAD), as revealed by use of the Mini International Neuropsychiatric Interview-Plus, Version 5.0.0. (MINI; Korean version).[18] The MINI is a brief, structured interview based on DSM-IV criteria[19] and is recommended to screen for psychiatric comorbidity in patients with headaches.[20] The kappa values of current MDD and GAD in the Korean version were 0.71 and 0.57, respectively, which exhibited good agreement between the MINI scores and expert diagnoses.

Statistical Analyses

The Statistical Package for the Social Sciences (SPSS version 21.0) software was used for data analyses. All descriptive data are presented as counts,

percentages, means, and standard deviations. First, GPower (G*Power 3.1.9) was used to calculate the proper sample size for the study. For the multivariate logistic regression model intended to be used, the type I error (α), power, and effect size were set to 0.05, 95%, and 0.15, respectively. The total sample size was then calculated to be 222 if the number of predictors was 20.

To determine the predictive factors of cutaneous allodynia, a logistic regression model with cutaneous allodynia as the dependent variable was developed using a two-step procedure. First, univariate logistic regression analyses were used to test variables for potential association with cutaneous allodynia in patients with migraine. Second, all variables with a statistically significant univariate effect were entered into a multivariate logistic regression model, and a forward likelihood ratio test was chosen to assess differential contributions of individual variables to cutaneous allodynia. Results were reported as an odds ratio (OR) with 95% confidence intervals (CI), standardized regression coefficients (beta), and corresponding *P* values. Statistical significance levels were set at $P < .05$.

Results

A total of 413 consecutive patients with migraine who visited the headache clinics of the two centers were examined. Among them, 81 patients were excluded from the study for the following reasons: refusal to participate in the study (n = 32); probable migraine (n = 25); taking a preventive medicine within the prior month (n = 15); illiteracy (n = 7); or aged younger than 15 years (n = 2). Subsequently, 332 patients (51 men and 281 women; mean age ± standard deviation [SD]: 39.9 ± 13.2 years) completed the study, well above the 222 calculated to be needed by G*Power. Among the participants, 32 patients (9.6%) had migraine with aura and 300 patients (90.4%) had migraine without aura. EM was present in 192 patients (57.8%), CM in 140 patients (42.2%), and MOH in 65 patients (19.5%). All patients with MOH also presented with CM. Concurrent medical diseases were present in 118 patients (35.5%), including hepatic and gastrointestinal disorders (n = 37), endocrine-related disorders (n = 35), hypertension and cardiovascular disorders (n = 15), otorhinolaryngologic disorders (n = 10), immune-related disorders (n = 10), orthopedic diseases (n = 8), neurologic diseases (n = 3), and others (n = 10). Photophobia, phonophobia, and osmophobia were present in 159 (47.8%), 209 (62.9%), and 150 (45.2%) patients, respectively. Current MDD and current GAD were identified in 73 (21.9%) and 59 patients (17.7%).

According to the ASC-12, 48 patients (14.5%) met the criteria for cutaneous allodynia. Demographic and clinical aspects of patients with migraine with respect to cutaneous allodynia are listed in Table 1. Patients with cutaneous allodynia had a higher proportion of female gender, higher frequency of CM, higher frequency of MOH, higher VAS scores (VAS max and VAS now), higher frequency of having photophobia or phonophobia, and higher mean MIDAS scores than those without cutaneous allodynia ($P < .05$, respectively). Also, the proportion of migraine patients with MDD was higher for cutaneous allodynia (54.2%; 26 of 48) than for those without (16.5%; 47 of 284), as was the proportion of patients with GAD (37.5% [18 of 48] with cutaneous allodynia vs 14.4% [41 of 284] without) ($P < .01$, respectively). Factors contributing to cutaneous allodynia, as assessed by univariate analyses, are shown in Table 2. Patients with cutaneous allodynia, when compared to those without, were more likely to have the following: female gender (OR = 4.796; 95% CI = 1.126–20.420; $P = .034$), CM (OR = 4.590; 95% CI = 2.324–9.066; $P = .000$), MOH (OR = 2.398; 95% CI = 1.222–4.707; $P = .011$), higher VASmax score (OR = 1.227; 95% CI = 1.033–1.457; $P = .020$), higher VASnow score (OR = 1.233; 95% CI = 1.098–1.384; $P = .000$), photophobia (OR = 2.759; 95% CI = 1.435–5.304; $P = .002$), phonophobia (OR = 3.402; 95% CI = 1.536–7.536; $P = .003$), higher MIDAS grade (OR = 3.609; 95% CI = 1.771–7.357; $P = .000$), current MDD (OR = 5.959; 95% CI = 3.116–11.396; $P = .000$), and current GAD (OR = 3.556; 95% CI = 1.817–6.960; $P = .000$).

Risk factors contributing to cutaneous allodynia as determined by multivariate analyses are documented in Table 3. The strongest predictor for cutaneous allodynia was current MDD (adjusted OR [AOR] = 4.552; 95% CI = 2.300–9.007, $P = .000$), followed by CM (AOR = 3.666; 95% CI = 1.787–7.521; $P = .000$) and photophobia (AOR = 2.707; 95% CI = 1.340–5.469; $P = .005$). A forward likelihood ratio test produced a four-variable model accounting for 24.9% of the variance in the dataset among patients with cutaneous allodynia.

Discussion

The present study found that 14.5% of patients with migraine had cutaneous allodynia during a migraine attack. Notably, this frequency was much lower than those observed in studies of Western patients.[2,3,7–9] In a US-based study, the frequency of observed cutaneous allodynia assessed by quantitative sensory testing (QST) was 79%,[2] and the frequency of self-reported cutaneous allodynia ranged from

Table 1 Demographic and Clinical Characteristics of Eligible Subjects (n = 332) with Respect to Cutaneous Allodynia (CA)

	Mean ± SD (range) or proportion (%)		
Characteristic	CA (n = 48)	No CA (n = 284)	Total (n = 332)
Age	41.25 ± 12.89 (17–60)	39.69 ± 13.24 (15–73)	39.91 ± 13.24 (15–73)
Gender, female	46 (95.8)	235 (82.7)	281 (84.6)*
Education, y	12.21 ± 2.52 (6–18)	12.82 ± 2.98 (3–18)	12.73 ± 2.93 (3–18)
Concurrent medical disease	23 (19.5)	95 (80.5)	118 (100)
Type of migraine			
Migraine with aura	1 (3.1)	31 (96.9)	32 (100)
Migraine without aura	47 (15.6)	253 (84.3)	300 (100)
Migraine chronicity			
EM	13 (6.7)	179 (93.2)	192 (100)*
CM	35 (25)	105 (75)	140 (100)*
Family history of migraine	31 (15.1)	174 (84.9)	205 (100)
MOH	16 (24.6)	49 (75.4)	65 (100) *
Age of onset	30.71 ± 11.67 (13–50)	30.22 ± 12.52 (7–60)	30.29 ± 12.38 (7–60)
Disease duration	10.56 ± 7.71 (0.3–30)	9.43 ± 7.95 (0.2–37)	9.59 ± 7.92 (0.2–37)
Migraine attack frequency (past 3 months)	19.23 ± 24.21 (1–90)	14.31 ± 16.93 (1–90)	15.02 ± 18.2 (1–90)
VASmax[a]	8.38 ± 2.03 (0–10)	7.59 ± 2.13 (0–10)	7.7 ± 2.13 (0–10)*
VASnow[b]	3.1 ± 2.27 (0–8)	1.74 ± 2.35 (0–10)	1.94 ± 2.38 (0–10)*
Accompanying symptoms			
Photophobia	33 (20.7)	126 (79.2)	159 (100)*
Phonophobia	40 (19.1)	169 (80.9)	209 (100)*
Osmophobia	27 (18)	123 (82)	150 (100)
MIDAS score	47.96 ± 44.74 (0–190)	20.82 ± 26.32 (0–181)	24.75 ± 31.11 (0–181)*
MIDAS grade			
Grades I and II	11 (7.2)	141 (92.8)	152 (100)
Grades III and IV	37 (20.5)	143 (79.4)	180 (100)
Current MDD	26 (35.6)	47 (64.4)	73 (100)*
Current GAD	18 (30.5)	41 (69.5)	59 (100)*

EM = episodic migraine; CM = chronic migraine; MOH = medication overuse headache; VAS = visual analog scale; MIDAS = Migraine Disability Assessment Scale; MDD = major depressive disorder; GAD = generalized anxiety disorder.
[a]Maximal headache intensity during the preceding 3 months. [b]Headache intensity on the day of psychiatric interviews.
**P* value < .05.

Table 2 Factors Associated with Cutaneous Allodynia by Univariate Analyses

Variable	β	SE (β)	OR (95% CI)	*P* value
Age	0.099	0.012	1.009 (0.986–1.033)	.449
Gender	1.568	0.739	4.796 (1.126–20.420)	.034
Education	−0.069	0.052	0.933 (0.843–1.033)	.181
Concurrent medical disease	0.604	0.315	1.830 (0.987–3.394)	.055
Type of migraine	1.751	1.028	5.759 (0.767–43.218)	.089
CM	1.524	0.347	4.590 (2.324–9.066)	.000
Family history of migraine	0.142	0.325	1.153 (0.609–2.182)	.662
MOH	0.875	0.344	2.398 (1.222–4.707)	.011
Age at onset	0.003	0.013	1.003 (0.979–1.028)	.800
Disease duration	0.017	0.019	1.017 (0.980–1.056)	.360
Migraine attack frequency	0.013	0.007	1.013 (0.998–1.027)	.088
VASmax[a]	0.205	0.088	1.227 (1.033–1.457)	.020
VASnow[b]	0.209	0.059	1.233 (1.098–1.384)	.000
Photophobia	1.015	0.334	2.759 (1.435–5.304)	.002
Phonophobia	1.244	0.406	3.402 (1.536–7.536)	.003
Osmophobia	0.521	0.315	1.683 (0.908–3.118)	.098
MIDAS grade	1.283	0.363	3.609 (1.771–7.357)	.000
Current MDD	1.785	0.331	5.959 (3.116–11.396)	.000
Current GAD	1.269	0.343	3.556 (1.817–6.960)	.000

SE = standard error; OR = odds ratio; CM = chronic migraine; MOH = medication overuse headache; VAS = visual analog scale; MIDAS = Migraine Disability Assessment Scale; MDD = major depressive disorder; GAD = generalized anxiety disorder.
[a]Maximal headache intensity during the preceding month.
[b]Headache intensity on the day of psychiatric interviews.

Table 3 Factors Contributing to Cutaneous Allodynia by Multivariate Analyses

Variable	β	SE (β)	Adjusted OR (95% CI)	*P* value
Constant	−0.235	0.314	0.790	.453
Current MDD	1.516	0.348	4.552 (2.300–9.007)	.000
CM	1.299	0.367	3.666 (1.787–7.521)	.000
Photophobia	0.996	0.359	2.707 (1.340–5.469)	.005

MDD = major depressive disorder; CM = chronic migraine.
*Standardized regression coefficients.

63.2% to 68%.[2,3] Additionally, multicenter and large cohort, clinic-based studies in the Netherlands and in the US reported cutaneous allodynia frequencies from 60% to 70%.[8,9] However, the frequencies of cutaneous allodynia observed in clinic-based studies was much lower in studies originating from Taiwan (17% to 48%).[10] Thus, the present study showed a trend similar to that in studies of Taiwanese patients with respect to cutaneous allodynia frequency. The definition of cutaneous allodynia and its classification of severity in this study were in accordance with the ASC-12 used by Lipton et al,[3] a validated quantitative tool for cutaneous allodynia assessment in patients with migraine. Using the ASC-12, Lipton et al reported that cutaneous allodynia was present in approximately 63.2% of migraine sufferers in the population,[3] a number remarkably consistent with estimates based on QST in clinical samples.[2]

The presence of cutaneous allodynia is associated with many migraine-related features. Several studies have reported that disease duration, attack frequency and disability, migraine with aura, lateralization of pain, presence of nausea or vomiting, and phonophobia/photophobia were associated with cutaneous allodynia.[2,3,8] Similar results were found from the univariate analyses of the present study. It was also found that the likelihood of cutaneous allodynia was increased in patients with migraine who were female, had photophobia, phonophobia, MOH, and CM. Additionally, the risk of developing cutaneous allodynia increased with the severity of headache-related disability and headache intensity. Unlike some previous studies, which reported migraine with aura as a predictor for cutaneous allodynia,[8,10] this study found no such significant association: only 32 of 332 patients (9.6%) in the current sample had migraine with aura, and only 1 of those was among the 48 patients with cutaneous allodynia (2.1%). This very small sample size might be the reason that having migraine with aura was not identified as a predictor of cutaneous allodynia.

The data of the study are not population based, so selection bias may also be one of the causes of the low proportion of migraine with aura. However, in both epidemiologic and clinic-based studies in Korea, the proportion of migraine with aura was below 10%,[21,22] which was consistently much lower than that observed in Western studies (38% to 61%).[2,3,7–9] Therefore, ethnic differences that affect migraine type may be related to the low prevalence of cutaneous allodynia observed in this study. Previous population-based[3,9] or multicenter studies[8] have reported that disease duration was one of the risk factors for cutaneous allodynia, but the present study found no such association. Differences in study design (population based vs clinic based) and sample size might explain the discrepancy in findings.

In the present study, the risk of developing cutaneous allodynia increased by a factor of 3 to 6 among patients with migraine who had current MDD or GAD. Current MDD and GAD were present in 54.2% and 37.5% of the migraine patients with cutaneous allodynia, respectively, which were higher rates than for patients without cutaneous allodynia (16.5% and 14.4% for MDD and GAD, respectively). Previous studies have also reported that comorbid depression and anxiety were more frequently observed in migraine patients with cutaneous allodynia than in those without, with depression and anxiety frequencies of approximately 67% and in the range of 36% to 73.3%, respectively.[8,10] Comorbid depression and anxiety were also associated with the severity of cutaneous allodynia.[11] A recent study reported that 45% of patients with migraine had depression over the course of their lifetimes and cutaneous allodynia was associated with a higher prevalence of depression.[9] After adjusting for covariates by multivariate analyses, the present study found that the most significant contributing factor for cutaneous allodynia was current MDD.

Although the putative mechanisms underlying the relationship between cutaneous allodynia, migraine chronicity, and depression are unknown, several studies have suggested potential explanations. Repetitive trigeminovascular neuron activation and subsequent repetitive modulatory pain pathway activation via the periaqueductal gray matter may cause periaqueductal gray matter impairment or neuronal loss, leading to migraine modulation and chronicity.[23] Some neurotransmitters might also be involved in

both psychiatric disorders and the nociceptive system. In a rat model of cutaneous allodynia, decreased tactile threshold was also associated with depression-like behavior; additionally, biogenic amines, such as dopamine, norepinephrine, and serotonin, were reduced in the spinal cord, thalamus, and prefrontal cortex of these animals.[24] Furthermore, serotonergic dysfunction in patients with depression (as demonstrated by reduced clomipramine responsiveness) was associated with decreased pain sensitivity and altered pain perception.[15] Thus, chronic repetitive central sensitization and dysfunction of central inhibition might be underlying mechanisms producing cutaneous allodynia.

Interestingly, in the present study, photophobia remained a significant predictor of cutaneous allodynia after adjusting for other covariates. The association between cutaneous allodynia and photophobia is not straightforward, although one possible connection is a common neural pathway for cutaneous allodynia and other sensory hypersensitivities. In a recent study describing the mechanisms of photophobia, neuronal activity in the posterior and lateral posterior thalamic trigeminovascular system (which mediates somatic cutaneous allodynia during a migraine attack) increased dramatically under ambient illumination. These thalamic neurons integrate visual input from photosensitive retinal ganglion cells and meningeal nociceptive signals and then pass the integrated signals to the somatosensory cortices.[25] Therefore, cutaneous allodynia and photophobia both appear to be mediated via thalamocortical projections and might originate through a central integrative system rather than from distinct afferent pathway dysfunctions. However, further studies are needed to clarify these relationships.

The present study had some limitations. First, the cross-sectional design of the study limited determination of the causal relationship between cutaneous allodynia and associated factors. A longitudinal study is needed to more precisely assess the causality of cutaneous allodynia development. Second, this was a hospital-based study, and the results may not be representative of the general population due to an inherent selection bias. Also, the rates of comorbidities tend to be higher in clinic-based studies than in population-based studies. The proportion of patients with CM (more than half) in the present study was much higher than that observed in the general population in Western countries (1.4% to 2.2%).[26] This suggests that an even lower frequency of cutaneous allodynia in the general Korean population with migraine would be expected, presuming that CM was one of the risk factors for cutaneous allodynia. Finally, the study did not use an objective test to measure cutaneous allodynia, such as the QST in another study.[2] Thus, the use of subjective reports of symptoms may result in differences in findings from studies using more objective cutaneous allodynia measurements.

This study design also had some particularly noteworthy strengths. It is the first study to investigate the prevalence and predictors of cutaneous allodynia in Korean patients with migraine. Based on the findings reported in the study, future plans to deal with patients having cutaneous allodynia will be established in Korea. Moreover, comorbid psychiatric diseases were assessed with a psychiatric interview using the MINI,[18] a highly reliable assessment tool for psychiatric disorders. Many studies evaluating psychiatric complications in patients with migraine have used self-report questionnaires, which only measure symptoms that might be affected by pain severity or migraine chronicity. However, psychiatric disorders are often independent of and less affected by such factors. The measurement methods used in the present study were therefore highly useful in elucidating the relationship between psychiatric disorders and cutaneous allodynia.

Conclusions

Cutaneous allodynia was not a common symptom in the Korean patients with migraine investigated in the present study. However, when present, cutaneous allodynia clearly has detrimental effects on patients with migraine.[4,5] Clinicians treating patients with migraine should therefore examine for the presence of cutaneous allodynia and attempt to provide specific therapeutic interventions for these symptoms. Such clinical approaches could additionally include the treatment of depression and migraine-associated features. A longitudinal study clarifying the effect of antidepressants or behavioral therapy on cutaneous allodynia is therefore highly warranted.

Acknowledgments

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