No association between migraine frequency, white matter lesions and silent brain infarctions: a study in a series of women with chronic migraine

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Keywords: brain magnetic resonance imaging, migraine, migraine aura, silent brain infarctions, vascular risk factors, white matter lesions

Background and purpose: It has been suggested that silent infarctions (SIs) and hyperintense white matter lesions (WMLs) are related to migraine frequency. We studied their prevalence and anatomical distribution in patients with chronic migraine (CM).

Methods: A total of 96 women with CM [mean age 43 (range 16–65) years] and 29 women with episodic migraine (EM) [mean age 36 (range 16–58) years] underwent 1.5-T magnetic resonance imaging following the CAMERA protocol. The number, size and location of SIs and deep WMLs were recorded and a modified Fazekas scale was applied to assess periventricular WMLs.

Results: White matter lesions were found in 59 (61.5%) women with CM and 17 (58.6%) women with EM (odds ratio, 1.13; 95% confidence intervals, 0.48–2.62; \( P = 0.784 \)). The majority (63% CM and 71% EM) were small deep WMLs. Exclusive periventricular WMLs were exceptional. Of the 739 WMLs seen in patients with CM, 734 (99.3%) were hemispheric and mostly frontal (81%). Posterior fossa WMLs were seen in only five (5.2%) women with CM (always in the pons) and two (6.9%) women with EM. Age >45 years was the only vascular risk factor associated with a higher WML number (median: 0 < 45 years and 3 > 45 years; \( P = 0.004 \)). We found seven SIs in six women with CM (6.3%).

Conclusions: As compared with the expected prevalence at this age, this study confirms that the prevalence of WMLs, in most cases small, deep and frontal, was increased in CM and EM. However, our results do not support an association of WMLs or SIs with a higher frequency of attacks, but with the presence of vascular risk factors and mainly age >45 years.

Introduction

Although migraine is associated with a relevant burden, it has traditionally been viewed as a condition without long-term consequences. Migraine, however, is considered an independent vascular risk factor (VRF), especially in young women with migraine with aura [1,2].

Magnetic resonance imaging (MRI) series have found that migraineurs are at increased risk of brain abnormalities of unknown pathophysiology and clinical significance, such as white matter lesions (WMLs) and silent infarctions (SIs). It has been suggested that SI and WML prevalence has a direct relationship with attack frequency [3–7]. The CAMERA study showed that migraineurs had a sevenfold increased risk of posterior fossa SI and that this risk increased with...
attack frequency [odds ratio (OR), 15.8 with >1 attack/month] [5–7]. We did not reproduce these findings in chronic migraine (CM) [8]. Kruit et al. also found that, among women with migraine, the risk of deep WML (dWML) load was significantly increased and that it increased with attack frequency (OR, 2.6 with> 1 attack/month) [4].

These findings raise concerns about the consequences of migraine, specifically in women with a high frequency of attacks. In this work, our aim was to address this point by analyzing the presence and distribution of WMLs in a series of women with CM.

**Patients and methods**

**Patients**

We included consecutive women aged between 16 and 65 years diagnosed as having CM [9] and recruited a group of women with episodic migraine (EM).

We excluded pregnant or breast-feeding women and those with excessive use of alcohol and serious active psychiatric or somatic disorders. We specifically excluded patients with a stroke history, but patients with the psychiatric comorbidities commonly seen in migraine (anxiety and depression) or fibromyalgia were not excluded.

Detailed charts and calendars were available for every participant. VRFs, including age >45 years, arterial hypertension, hypercholesterolemia, smoking, history of aura and analgesic overuse [9] were obtained. All subjects underwent a general and neurological examination. The study was approved by the institutional board and participants gave their written consent.

**Magnetic resonance imaging protocol**

The MRI studies were acquired on a 1.5-T unit (Signa LX 9.1; GES, Greenville, WI, USA) using a standard quadrature head coil and following the CAMERA-I protocol [4]. Brain images were acquired with 40 contiguous, 3-mm axial slices (field of view, 22 cm; matrix, 192 × 256). Sequences included fluid-attenuated inversion recovery (FLAIR) [TR (repetition time)/TE (echo time)/TI (inversion time)/NEX (number of excitations), 8000/120/2000/1 and DP (proton density)/T2/TR/TE/NEX/echo-train length, 2100/12.5-76/2/6]. In addition, 20 5-mm, sagittal brain images (fast T1 FLAIR; TR/TE/T1/NEX, 1800/7.7/750/2) were acquired as part of the routine protocol, but not included in the analysis.

Two neuroradiologists (A.M. and E.S.) blinded to diagnosis (CM or EM) rated SIs and WMLs on hard copies. A third neuroradiologist (A.S.) made the final diagnosis in cases in which the raters disagreed. Infarcts were defined as non-mass parenchymal defects, with a vascular distribution, isointense to cerebrospinal fluid signal on all sequences and, when supratentorial, surrounded by a hyperintense rim on FLAIR and proton-density images (Fig. 1). The number, location and size of infarcts were recorded. Virchow–Robin spaces were excluded as infarcts based on location, shape, size and absence of a hyperintense border [10]. To determine whether there was preferential damage to any one vascular system, we scored infarcts by location and vascular supply. Topographical maps were used to define four categories that reflected the two major territories of blood supply to the brain (anterior circulation and posterior circulation) and two areas with a heterogeneous blood supply (basal ganglia and corona radiata/centrum semiovale) [11]. Posterior circulation SIs were classified as supratentorial and infratentorial. The infratentorial SIs were further subclassified as either territorial or junctional according to previously reported criteria and following Kruit et al. [4]. Territorial lesions occupied the territory of the posterior inferior cerebellar artery, the medial or lateral branches of the posterior inferior cerebellar artery, the territory of the superior cerebellar artery, the medial and lateral branches of the superior cerebellar artery or the territory of the anterior inferior cerebellar artery. Junctional lesions were located at the boundary region (defined as ≤5 mm from the indicated border in the template) between two territories.

The WMLs had to be hyperintense on all sequences and were divided into periventricular WMLs (pWMLs) and dWMLs. Both were evaluated following CAMERA-I methodology. pWMLs were evaluated with the Fazekas semiquantitative scale [12], which evaluates pWMLs globally, but we modified it to be applied in three regions: adjacent to anterior (frontal) horns, walls of the lateral ventricles (bands) and occipital horns. pWMLs were assessed in these three regions and rated as 0 (no pWMLs), 1 (pencil-thin lining), 2 (smooth halo or thick lining) or 3 (large confluent lesions). The three regional scores were added for the final score (0–9). dWMLs were rated by lobe location, number and size, as measured with a caliper on the FLAIR image (Fig. 2). The WML count was combined to obtain a measure of load by multiplying each lesion by a size-dependent constant [0.0042 mL for small (≤3 mm) lesions, 0.114 mL for medium (4–10 mm) lesions and 0.9 for large (>10 mm) lesions]. All values of the lesioned volume were grouped and divided into quintiles; a volume in the superior quintile was considered as ‘high load’.
Data analysis

Continuous variables are given as mean ± SD with minimum and maximum values. They were compared by using standard parametric Student–Welch or non-parametric Mann–Whitney tests, depending on the distribution normality. Categorical variables are given as absolute and relative frequencies. The exact proportion test was used to test the equality among the groups. Crude and adjusted ORs were used as effect size measures. The relationship between the number of WMLs and headache frequency was studied through linear regression. \( P < 0.05 \) was considered significant. Analyses were carried out with software R 3.1 (www.r-project.org). We followed the STROBE statement (https://www.strobe-statement.org/index.php?id=strobe-home) and therefore no multiple testing corrections have been made.

Results

We included 96 women with CM [mean age 43 (range 16–65) years] and 29 women with EM [mean age 36 (range 16–58) years; \( P = 0.015 \)]. These numbers allow significance to be demonstrated (with standard type I error of 5%) 80% of the time (type II error of 0.2) with differences above 30%. The average length of time for which patients had CM was 8.4 (range 1–38) years. A history of aura was obtained in 48 (50%) patients with CM and 15 (51.7%) patients with EM. Only five patients with CM and two patients with EM exhibited aura in more than 50% of attacks in the last year. Comorbidities, VRFs and treatments are shown in Table 1.

White matter lesions

A total of 76 migraineurs (60.8%) had at least one WML. WMLs were found in 59 (61.5%) women with CM and 17 (58.6%) women with EM [\( P = 0.517; \) crude OR, 1.43; 95% confidence intervals (CI), 0.49–4.18]. The OR adjusted by individual VRF ranged between 1.04 (95% CI, 0.44–2.44) and 1.11 (95% CI, 0.47–2.61). Adjusting by number of VRFs, age and comorbidities, the OR was 0.94 (95% CI, 0.28–3.15). Time of evolution of CM was associated with a higher
risk of WMLs (OR, 1.09; 95% CI, 1.02–1.18); however, this effect disappeared when adjusted by the number of VRFs, age and additional comorbidities (OR, 1.02; 95% CI, 0.94–1.10). The majority were dWMLs (63% for CM and 71% for EM). A total of 22 patients (22.9%) with CM and 5 (17.2%) patients with EM had pWMLs (P = 0.942; crude OR, 1.03; 95% CI, 0.28–3.15; adjusted OR, 0.70; 95% CI, 0.27–1.85, respectively). Exclusive pWMLs were exceptional; they were detected in only two women with CM and in no women with EM (P = 1.00). The most frequent location for pWMLs was around anterior horns (90.9% in women with CM and 100% in women with EM), followed by posterior horns (54.5% in CM and 20% in EM) and ventricular bands (40.9% in CM and 0% in EM). None were significant due to the low number of cases. Even though final scores on the Fazekas scale were numerically, on average, higher for CM (0.6) as compared with EM (0.2), differences were not significant (P = 0.432) and exactly 50% in both groups had a 0 score in this scale. No differences were found when patients were classified into three categories according to their scores on the modified Fazekas scale (0, no lesions; 77.1% of patients with CM vs. 82.8% patients with EM; 1–2, mild load: 12.5% of patients with CM vs. 17.2% patients with EM; 3–9, moderate to severe load: 10.4% of patients with CM vs. 0% of patients with EM) (P = 0.671). Table 2 shows crude and adjusted ORs. Age, VRFs and other comorbidities (yes/no) were included in the models. To further analyze a potential association between migraine frequency and WMLs, we performed a regression analysis considering the average number of headache days in the 3 months previous to the MRI study in each patient. WMLs were not affected by medications. The median number of WMLs in those who were taking symptomatic or preventative treatment and in those who were not taking these drugs was 1 in both cases (P = 0.260 for symptomatic treatment; P = 0.762 for preventatives). Differences in the median number of WMLs in those who were using or not using non-steroidal anti-inflammatory drugs (NSAIDs), triptans, beta-blockers, topiramate or amitriptyline were < 2 (P > 0.2). The regression coefficient for WMLs/frequency of headache days was 0.15 (95% CI, −0.26 to 0.55) (P = 0.477; r² = 0.008, respectively). When adjusted by covariables, the regression coefficient was 0.10 (95% CI, −0.3 to 0.52) (P = 0.362; r² = 0.085).

We saw dWMLs in 57 women (59.4%) with CM and in 17 (58.6%) women with EM (P = 0.784; crude OR, 1.13; 95% CI, 0.48–2.62; adjusted OR, 0.73; 95% CI, 0.27–1.94). With regard to dWMLs, the average number was 7.7 (range 0–177) in CM (total 739) and 3.2 (0–27) in EM (total 93) (P = 0.078), most of small size. In both groups, 50% of patients showed 0 or 1 lesions. Of the 832 WMLs, 734 (88.2%) were hemispheric, frontal being the most common (80.6% in CM and 82.8% in EM), followed by parietal (14.7% in CM and 14.0% in EM), temporal (3.8% in CM and 1.1% in EM) and occipital (0.1% in CM and 0% in EM). At least one frontal lesion was seen in 57 (59.3%) women with CM and in 15 (51.7%) women with EM. The average number of frontal dWMLs in CM was 10.5 vs. 5.1 in EM (P = 0.065). dWML prevalence in terms of size did not significantly differ between CM and EM (large lesions, 6.3% vs. 3.4%; medium lesions, 43.8% vs. 31.0%; small lesions, 53.1% vs. 51.7%). We did not find significant differences between CM and EM in the proportion of large

| Table 1 Summary of main comorbidities and potential vascular risk factors (VRFs) of women with chronic migraine (CM) and episodic migraine (EM) included in this study |
|-----------------|-----------------|-----------------|-----------------|
|                | CM (n = 96)     | EM (n = 29)     | P-value         |
| Depression     | 43 (44.8%)      | 2 (6.9%)        | <0.001          |
| Fibromyalgia   | 14 (14.6%)      | 0               | 0.065           |
| Hypothyroidism | 3 (3.1%)        | 0               | 0.786           |
| Asthma         | 6 (6.3%)        | 0               | 0.377           |
| Aura           | 48 (50.0%)      | 15 (51.7%)      | 1.000           |
| Age ≥45 years  | 46 (47.9%)      | 8 (27.6%)       | 0.085           |
| Arterial hypertension | 11 (11.5%)   | 1 (3.4%)        | 0.356           |
| Hypercholesterolemia | 18 (18%)   | 2 (13.3%)       | 0.216           |
| Diabetes       | 0               | 0               | –               |
| Obesity        | 6 (6.3%)        | 0               | 0.377           |
| Smoking        | 11 (11.5%)      | 2 (6.9%)        | 0.722           |
| VRFs ≥1        | 63 (65.6%)      | 4 (13.7%)       | <0.001          |
| VRFs ≥2        | 23 (24.0%)      | 1 (3.4%)        | 0.029           |
| Analgesic overuse | 34 (35.4%)  | 0               | <0.001          |
| NSAIDs         | 71 (74.0%)      | 23 (79.3%)      | 0.734           |
| Triptans       | 66 (68.8%)      | 16 (55.2%)      | 0.260           |
| Preventative treatment | 83 (86.4%) | 4 (13.8%)       | <0.001          |

NSAID, non-steroidal anti-inflammatory drug. Data are given as n (%).

| Table 2 Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CI) showing that white matter lesions (WMLs) are independent of the type of migraine (episodic migraine or chronic migraine) |
|-----------------|-----------------|-----------------|-----------------|
|                | Crude OR (95% CI) | P-value | Adjusted OR (95% CI) | P-value |
| WML            | 1.13 (0.58–2.62) | 0.784 | 0.73 (0.27–1.94) | 0.528 |
| pWML           | 1.43 (0.49–4.18) | 0.517 | 0.94 (0.28–3.15) | 0.924 |
| dWML           | 1.03 (0.28–3.15) | 0.942 | 0.70 (0.26–1.85) | 0.469 |
| pfWML          | 0.74 (0.14–4.04) | 0.729 | 0.71 (0.11–4.71) | 0.728 |

Adjusted models include age, additional comorbidities (yes/no) and vascular risk factor. dWML, deep WML; pfWML, posterior fossa WML; pWML, periventricular WML.
(3.2% vs. 1.1%) or medium (38.6% vs. 29.0%) size dWMLs, but the percentage of small size lesions was significantly higher (69.9% vs. 58.2%; \(P = 0.040\)) in women with CM vs. women with EM. In terms of dWML lesion load, there was no difference between CM and EM in any of the five quintiles. The low dWML load group was the most numerous (40.6% for CM and 41.4% for EM), whereas high dWML load was seen in 20.8% of the patients with CM vs. 17.2% of the patients with EM. Regardless of migraine type, pWML prevalence was higher in patients also showing dWMLs versus without dWMLs (33.8% vs. 3.9%; \(P < 0.001\)). Also, women with high dWML load had a higher prevalence of pWMLs as compared with those without high lesion load (52.0% vs. 14%; \(P < 0.001\)). pWML prevalence was higher in women with than in those without dWMLs, in both CM (35.1% vs. 5.1%; \(P < 0.001\)) and EM (29.4% vs. 0.0%; \(P < 0.001\)). Posterior fossa WMIs were seen in only five (5.2%) women with CM and two (6.9%) women with EM.

**Relationship between white matter lesions and vascular risk factors**

The prevalence of at least one VRF among women with dWMLs was 89.5% in the CM group and 70.6% in the EM group (\(P = 0.112\)). dWML prevalence was numerically different in those patients with at least one VRF versus those without VRFs in both CM (63.0% vs. 40.0%; \(P = 0.151\)) and EM (63.2% vs. 50.0%; \(P = 0.694\)).

When VRFs were analyzed separately, analgesic overuse was significantly more frequent in CM than in EM (35.1% vs. 0.0%; \(P = 0.004\)). Age >45 years, hypertension, hypercholesterolemia and smoking were more frequent in CM versus EM cases, but this was not significant (Table 1). Although overuse did not influence the presence of dWMLs, in both diagnostic groups dWML prevalence was higher in patients aged >45 years compared with those aged <45 years, although, due to the sample size, this difference was significant only in CM (76.1% vs. 44.0%; \(P = 0.002\)). dWMLs were numerically more frequent in CM in those with versus those without hypertension (81.8% vs. 56.5%) and in those with versus without a smoking habit (81.8% vs. 56.5%), but hypercholesterolemia (58.8% vs. 59.5%) or aura (56.3% vs. 62.5%) did not influence the number of dWMLs. Although the numbers for the EM group were lower, numerical data were superimposable.

Analyzing the subjects with high dWML load, dWML prevalence was significantly higher only in patients aged >45 years. These results were seen for both CM, where high load was found in 37.0% of those aged >45 years versus 6.0% in younger women (\(P < 0.001\)) and EM, where high load was found in 50.0% of women aged >45 years versus 4.8% in younger women (\(P = 0.013\)). Although a higher numerical prevalence of high lesion load was seen (for CM and EM) in women with versus without hypertension, hypercholesterolemia, smoking, overuse or aura was not associated with a higher numerical prevalence of high dWML load.

**Silent infarctions**

We found seven SIs in six women with CM (6.3%). Four were in the basilar territory: two in the pons, one in the cerebellum and one in the medial temporal lobe. The remaining three were two in the basal ganglia and one in the lateral temporal lobe. The infratentorial lesions were territorial. At least two VRFs were seen in five of these six patients with CM. No SI images were detected in the EM group. Five (83.3%) of the six patients with SIs also had WMLs; all five had dWMLs (four with high lesion load) and two also had pWMLs.

**Discussion**

Our data confirm that WML prevalence (60.8%) is increased in migraineurs when compared with that expected in the population [3,13], which should fall below 20% for the age group of our series [4]. WML prevalence, however, was similar in CM (61.5%) and EM (58.6%) and statistics did not show an association between migraine type or headache frequency and WMLs. Taking into account the headache frequency of the women with CM and their long history, these data do not support a relationship between the presence of these lesions and migraine frequency, as suggested mainly by the CAMERA-I study, which considered ‘high’ attack frequency to be \(\geq 1\) attack/month [4].

The SI prevalence in the CAMERA-I study was 8.1% for migraineurs (most in the posterior circulation) and 5.0% for controls. We found just seven SIs in six patients with CM (6.3%), three of them supratentorial. These results concur with those already reported by our group in patients with CM showing that frequency of migraine attacks itself is not a factor that increases posterior fossa SI lesion risk [8].

One of our aims was to analyze the anatomical distribution of these WMLs and to study its possible relationship with migraine frequency. Two population studies have investigated this point [4,15]. The majority of our patients with WMLs (62.8%) had exclusively dWMLs. Fewer than one-quarter of
patients with EM or CM had pWMLs and exclusive pWMLs were exceptional; they were detected in only two women with CM and in no women with EM. The anatomical distribution of pWMLs (anterior horns > posterior horns > ventricular bands) and the presence of a maximum of three lesions, as in nine out of 10 CM cases, are of help in the differential diagnosis between migraine and new-onset multiple sclerosis [15]. The most frequent location for pWMLs was around the posterior horns (90.9% in women with CM and 100% in women with EM), followed by the posterior horns and ventricular bands. pWML prevalence in the CAMERA-I study was 80.6% [4], much higher than our 22.9% and that of the EVA-MRI study [14]. As the methodology of this work is superimposable on that of the EVA-MRI study [14], the difference could be explained by the different origin of our series and, probably, by the higher proportion of VRFs and particularly age >45 years in the CAMERA series. In any case, these findings again do not support a relationship between pWMLs and migraine frequency.

Our prevalence of dWMLs (59.4%) was apparently higher than that found in the CAMERA (37%) and EVA-MRI (41%) studies. However, if, in line with the previous studies, we consider only dWMLs >4 mm, our prevalence of dWMLs decreases to 40.8% and concurs with previous reports. Only 20.8% of our CM cases exhibited high lesion load, lower than the 41.4% seen in the EVA-MIG study [14] and similar to the 22.0% found by Kruit et al. [4], which, again, does not support the suggestion that dWMLs directly correlate with attack frequency. By contrast, although not significant, the average number of dWMLs was higher in CM (7.7) than in EM (3.2) and the average global lesion load was also higher in the CM (0.6 mL) than in EM (0.01 mL). These differences, however, disappeared when VRFs, and especially age >45 years, were included in our analysis. These findings concur with series that strongly correlate these lesions with VRFs and particularly age >45 years [12,16,17]. Interestingly, a history of aura, in general and in both groups, was not associated with a higher dWML prevalence or lesion load. The effect of aura on dWMLs is controversial. Several studies have found a higher risk of stroke in patients with migraine with aura [14,19–24] and the EVA-MRI was able to find a significant association between dWMLs and migraine with aura [14]. However, data from this series, the CAMERA study [4] and a recent study [24] have not found a higher risk of dWMLs in migraine with aura. These differences should be clarified in larger series using a homogeneous approach to aura diagnosis.

The distribution of dWMLs in patients with CM and EM was coincidental and suggestive of a microvascular origin; both groups showed dWMLs of small size, supratentorial predominance and mostly located in the frontal lobes, which fits with the pattern described for WMLs of vascular origin [25]. It has been proposed that the poor degree of collaterals in the frontal deep white matter could explain its higher vulnerability to developing ischaemic lesions of small vessels [25,26]. The nature of pWMLs is more controversial. Classical studies have suggested that, considering its location and specific morphology (pencil-thin lining, smooth halo or thick lining), these lesions could be the result of dynamic cerebrospinal fluid abnormalities [27]. However, recent MRI studies, using white matter segmentation or three-dimensional mapping techniques, have not been able to confirm this hypothesis and suggest that both deep and periventricular lesions would share a common mechanism [28]. Our results, showing a clear association between the two types of lesions and a similar anatomical pattern (frontal for dWMLs and around anterior horns for pWMLs), make the hypothesis of a common mechanism more probable.

Several limitations deserve comment. Firstly, this was a clinic-based series and therefore not necessarily extrapolatable to the population. Second, the EM group was arguably rather small. Our objective was to test whether migraine frequency correlates with a higher number of WMLs, which was the reason for recruiting a larger CM sample. There are already enough data available from several published studies in the general population and patients with EM to be compared with our CM results for all variables analyzed. In fact, one of the reasons for including the EM group was to keep our neuroradiologists blind to their diagnosis. Finally, most of our patients used both acute and preventative treatment for their migraines and it is fair to recognize that their effect on WMLs is unknown. Although fewer than 5% of migraineurs in the CAMERA study took prophylactic therapy, most of our patients used preventative. It remains uncertain whether preventatives reduce the risk of infarct-like lesions and this could be a hypothetical explanation for our basically negative findings. There are, however, no solid arguments supporting this hypothesis, which seems unlikely considering the long duration of CM and the fact that the women included in this study were still meeting CM criteria when MRI was obtained according to their headache diary. However, most of our patients were using either NSAIDs and/or triptans as symptomatic medications. The relationship between NSAIDs/triptans and stroke risk is controversial.
Although some NSAIDs could theoretically be protective due to their potential antiplatelet actions [29], high and frequent doses of these drugs (as happens in CM) have been shown to increase the stroke risk [30,31]. In spite of the vasoconstrictor potential of triptans, there is no evidence that they increase the risk of infarct-like lesions [32] and our results, coming from patients with a high frequency of use of these medications, provide additional reassurance.

Our results indicate that it is premature to conclude that attack frequency itself further increases the presence of WMLs, which are already known to be more prevalent in the migraine brain. As the clinical significance of WMLs (or posterior fossa SIs) in terms of risk of recurrence of acute attacks of migraine remains obscure and controversial [33], routine MRI scans are not indicated in CM evaluation, but to rule out secondary forms of migraine, and priority should be given to addressing modifiable VRFs [34,35].

Acknowledgements

This work was supported by PI14/00020 FISSS grant (Plan Nacional I + D + I, Fondos Feder, ISCIII, Ministry of Economy, Spain).

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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