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RESEARCH ARTICLE

Daily Living Activities and Cognition in Aged Patients: Effect of Acute Systemic Diseases and Stroke on Leukoaraiosis

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Abstract: ***Background*:** Acute Systemic Diseases (ASD) impact on extended leukoaraiosis (ExL-A) have been seldom described. We study the deterioration in daily life activities (DLA) and cognition associated with ASD events compared with the well-described impacts of stroke in patients with leukoaraiosis (L-A).

***Methods*:** Cross-sectional surveys of aged adults from the emergency room after an acute event of ASD or stroke, hospitalized or receiving home care, were followed for one year. From 268 initial patients 206 were included in the study, all with moderate to severe L-A (Fazekas 2 and 3). The Clinical Deterioration Rating (CDR) and the modified Rankin scale with structured interview were obtained one week previous to admission and after 3 and 12 months of evolution. Comparisons were conducted within and between groups with nonparametric techniques.

***Results*:** We formed three groups of similar age, A: Inpatients with one Stroke, B: Inpatients with one ASD, and C: Outpatients with one ASD. A sudden deterioration in Rankin was evident in Group A, while in B and C impairment was progressive. Impairment in CDR was smooth in all groups while in Rankin it was always greater than in cognition (CDR). No differences were found in the associations between groups and risk factors, hypertension being the most frequent one.

***Conclusion*:** ASD in ExL-A causes a worsening of DLA and cognition similar to that observed in ExL-A with concomitant stroke indicating the need, in ageing patients, of differential diagnosis in order to achieve the best possible treatment.

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1. INTRODUCTION

Leukoaraiosis (L-A), also known as changes in white matter, is seen in brain Magnetic Resonance Images (MRI) in paraventricular areas, semioval centers and bulging areas of aged individuals, as bilateral, symmetric and irregular zones of hyperintensities in T2- weighted and FLAIR-IRMC.

Observed L-A in Computed Tomography (CT) images is used to denote these ischemic white matter type lesions [1], as opposed to those processes related to demyelization, such as infectious, toxic, metabolic, immune-mediated, hydrocephalus, or brain radiation therapy. L-A is associated with vascular risk factors, mainly arterial hypertension, diabetes and smoking among others and advanced age [2, 3].

A frequently described presentation in L-A is a stroke with the coexistence of ischemia of the small cerebral artery (Small Vessel Disease, SVD); age and functional impairment also being common [4]. L-A presents vascular lesions that may be asymptomatic or symptomatic [5]: hemorrhagic changes are more likely after a thrombolytic event [6], recurrent stroke [7] and post-stroke dementia [8]. In advanced age, L-A is also an indicator of DLA deterioration, without stroke [9].

The brain areas where the L-A is present show oxygen deficit [10], increase of carbon dioxide [11], extravasations of plasma and lesser regional flow [12]. Patients with Alzheimer's disease can also develop the L-A (mixed phenome-

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non), but the explanation for this relation still remains a matter of debate without a *consensus scholarum* yet.

Physical exercise promotes better circulatory conditions in the cerebral zones with L-A, preventing the early development of gait disorders and dementia [13-16].

Recently, the LADIS studies (L-A in European groups) have highlighted aspects of the functional impairment, such as, *inter alia*, gait disorders with a tendency to fall, urinary incontinence and different degrees of cognitive impairment [17, 18].

Until now the clinical impact of Acute Systemic Diseases (ASD) concomitant with extended L-A (ExL-A) has not been extensively studied, with the exception of some isolated cases. During hospitalization at the emergency room some of the main manifestations observed in L-A patients are the loss of normal gait with severe instability, postural abnormalities, falls and delirium.

In the present observational and prospective study, we compare the impact of an ASD event in ExL-A patients with the worsening in daily life activities and in cognition associated with the deterioration produced by a stroke, already analyzed extensively in the bibliography.

2. MATERIALS AND METHODS

A total of 268 aged Caucasians patients (between 65 and 95 years) with ExL-A and a stroke or an ASD event were recruited from the emergency room of the Hospital Sirio-Libanés, Universidad de Buenos Aires, between May 2015 and June 2016; the ensuing follow-up period was one year. Patients were not selected in any way, with the exception that those not willing or not able to undergo the process of informed consent (*e.g.,* confused and without a caregiver) were excluded.

Consultation symptoms were loss of locomotion and sphincters, falls, apraxia and agnosia, disorientation and delirium, and expression of a focal stroke deficiency. All patients included in this study had an ExL-A on the MRIs obtained on the first or second day of the acute event and was classified according to the Fazekas scale [19] as type 2 or 3. The MRIs were obtained with Magneton Siemens or Gyroscan Phillips equipment at 1.5 Tesla and reviewed by neuroradiologists blind to clinical manifestations. The sequences performed were T1, Fast Spin Echo, T2, FLAIR and diffusion, in sagittal, axial and coronal incidences. Acute lesions caused by a stroke were determined by the diffusion sequence, classifying infarcts as lacunar subcortical or extensive cortical. In the ASD groups, the presence of an acute stroke was discarded by the sequence of diffusion of MRI's which resulted negative for an acute vascular event.

Data from the 43 patients who died during the study were excluded from the analysis of results, as well as those from 19 patients who failed to attend the follow-up protocol. No significant differences between groups were found in the number of patients lost. Finally, 206 patients met the study criteria.

The present observational protocol was approved by the Local Ethics Committee of the Hospital and the patients and/or relatives signed an informed consent prior to the incorporation.

According to the concomitant pathology, three groups with ExL-A patients were formed. Group A: Hospitalized patients with one single stroke; Group B: Hospitalized patients with one ASD (such as: respiratory, urinary or gastrointestinal tract infections, dehydration, hyponatremia, anemia with less than 9 g% hemoglobin, coronary ischemia, bronchospasm with or without smoking, systolic and diastolic hypertension greater than 160/100, non-surgical intense abdominal pain, and other systemic diseases); and Group C: Outpatients with one ASD similar to Group B but with less clinical involvement not requiring hospitalization.

The DLA evaluation was performed with the modified Rankin scale, in a structured interview (mRSsi) [20] at the time of admission, obtained from a responsible caregiver, and referred to the DLA of the previous week. This evaluation was repeated at 3 and 12 months by the same person. Estimates of cognitive impairment and/or dementia were obtained using the Clinical Dementia Scale (CDR) [21]. Vascular dementia was defined according to the criteria of the consortium of Canada centers [22]. The Evans index [23] was used in the imaging analysis to diagnose normal pressure hydrocephalus. The depressive state was evaluated with the geriatric scale for depression (GDS) [24].

In the blood analysis, TSH, T3, T4, folic acid, vitamin B12 and serology for syphilis were monitored. In the case of hydrocephalus, severe depression or abnormalities in the above analyses, patients were not recruited in the study. Thus, all patients had values within the normal ranges in the lab blood analyses. No significant differences were found between groups. Vascular risk factors, *i.e.*, hypertension [25], diabetes mellitus, hyperlipidemia, smoking, and atrial fibrillation were recorded in all three groups.

Statistical analysis was performed on the variables measured at the time of their incorporation into the emergency room (baseline state), and 3 and 12 months later, applying non-parametric techniques between and within the 3 groups of patients formed from the 206 patients included. The 0.95 confidence intervals for the mean were calculated applying the simple bootstrap method [26] with 10000 resamples.

The incidence of vascular risk factors in the different groups was tested with the Chi square statistic ($\chi 2$) for differences between proportions. The Rankin and CDR comparisons between groups were conducted applying the Kruskal-Wallis non-parametric procedure to the median of each group under the null hypothesis of no difference between groups. The evolution of the variables was studied analyzing the sign of the changes of each individual within groups with the binomial test under the null hypothesis of no change. Notwithstanding that the number of observations on each group would have allowed for normal approximations, the slightly more conservative nonparametric equivalents were applied since these do not require strict assumptions while retaining enough power to detect differences.

3. RESULTS

Examples of Magnetic Resonance Images (MRI) in FLAIR sequences showing the brain lesions in ExL-A

(Fazekas 2-3) included in this protocol and lacunar and cortico subcortical infarcts are shown in Fig. (**1**).

The analysis of the numerical and statistical values of the tests performed in patients is presented in Table **1**. In the upper part of Table **1**, the demographic and risk factors are compared. No significant differences were found in relation to age, sex, vascular risk factors and dementia, thus the three groups might be considered comparable with regard to known risk factors and, as shown in Table **1**, hypertension appears with the highest frequency. The comparisons and evolution of Rankin and CDR presented in the figures are based on percentages of the mean value of the variables in each group and calculated applying, for example, the formula: 100 x (Deterioration of Group A - Deterioration of Group B) / Deterioration of Group B).

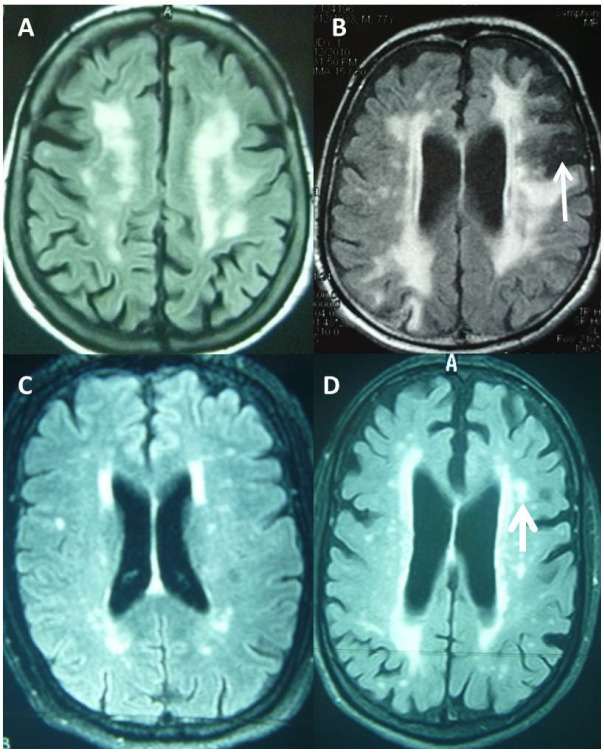

Fig. (1). FLAIR and MRI sequences. **A)** Severe leukoaraiosis (Fazekas 3) in a patient without stroke with extension to the periventricular regions and semioval centers, in the latter's the most affected are the frontal lobes and bilaterally the parietal lobes. **B)** Severe leukoaraiosis, extended to the periventricular regions and semioval centers, in a patient with stroke and great infarct lesion (white arrow) in frontal and parietal lobes. **C)** Moderate leukoaraiosis (Fazekas 2) in a non-stroke patient with localized lesions in the periventricular regions and low microangiopathic hyperintensity; semioval centers are not compromised. **D)** Moderate leukoaraiosis in a patient with lacunar stroke (white arrow=contiguous to the leukoaraiosis) with lesions localized in peri and paraventricular regions and hyperintense lesions of the small vessels, the semioval centers are not compromised.

Table 1. Demographic and experimental data.

Variable	GROUP A	GROUP B	GROUP C	Differences
OBSERVATIONS	*n*=86 (44 F /42 M)	*n*=78 (37 F /41M)	*n*=42 (19 F /23 M)	
MEAN AGE *	77.9 ± 7.2	78.8 ± 7.6	79.1 ± 8.9	
VASCULAR RISK FACTORS				CHI SQUARE TEST:
Hypertension	*n* = 64 (74.4%)	*n* = 51 (65.4%)	*n* = 25 (59.5%)	$\chi^2 = 3.26$; $p = 0.196$
Type 2 Diabetes	*n* = 26 (30.2%)	*n* = 26 (33.3%)	*n* = 12 (28.6%)	$\chi^2 = 0.34$; $p = 0.845$
Hyperlipidemia	*n* = 33 (38.4%)	*n*= 33 (42.3%)	*n* =10 (23.8%)	$\chi^2 = 4.15$; $p = 0.125$
Tobacco	*n* = 12 (13.9%)	*n*= 10 (12.8%)	*n*= 10 (23.8%)	$\chi^2 = 3.29$; $p = 0.123$
Atrial Fibrillation	*n* = 17 (19.8%)	*n* = 16 (20.5%)	*n* = 7 (16.7%)	$\chi^2 = 0.27$; $p = 0.874$

(Table 1) Contd…

Variable	GROUP A	GROUP B	GROUP C	Differences
DEMENTED Subjects	n = 31 (36.0%)	n = 30 (38.5%)	n = 15 (35.7%)	$\chi^2 = 0.13$; $p = 0.935$
RANKIN Values †				KRUSKAL-WALLIS TEST:
Basal	1.23 - 1.66 - 2.15	1.16 - 1.46 - 1.78	0.62 - 1.07 - 1.62	Group A *vs*. Group B; $p = 0.060$
				Group A *vs*. Group C; $p < 0.001$
				Group B *vs*. Group C; $p = 0.110$
3 Months	2.67 - 3.22 - 3.78	2.01 - 2.41 - 2.79	1.31 - 1.81 - 2.33	Group A *vs*. Group B; $p < 0.001$
				Group A *vs*. Group C; $p < 0.001$
				Group B *vs*. Group C; $p = 0.005$
Impairment (%)	+ 93.69	+ 64.84	+ 69.00	Group A *vs*. Group B; $p = 0.039$
				Group A *vs*. Group C; $p < 0.001$
				Group B *vs*. Group C; $p = 0.141$
12 Months	3.38 - 3.87 - 4.29	3.29 - 3.67 - 4.05	2.70 - 3.24 - 3.76	Group A *vs*. Group B; $p = 0.870$
				Group A *vs*. Group C; $p = 0.832$
				Group B *vs*. Group C; $p = 0.830$
Impairment (%)	+ 132.83	+ 150.82	+ 202.03	Group A *vs*. Group B; $p = 0.870$
				Group A *vs*. Group C; $p = 0.832$
				Group B *vs*. Group C; $p = 0.830$
CDR Values †				
Basal	0.38 - 0.74 - 1.13	0.36 - 0.67 - 0.99	0.24 - 0.50 - 0.84	Group A *vs*. Group B; $p = 0.673$
				Group A *vs*. Group C; $p = 0.702$
				Group B *vs*. Group C; $p = 0.494$
3 Months	0.97 - 1.36 - 1.75	0.61 - 0.90 - 1.20	- 1.06 - 1.44	Group A *vs*. Group B; $p = 0.090$
				Group A *vs*. Group C; $p = 0.323$
				Group B *vs*. Group C; $p = 0.600$
Impairment (%)	+ 82.20	+34.32	+112.00	Group A *vs*. Group B; $p < 0.001$
				Group A *vs*. Group C; $p = 0.643$
				Group B *vs*. Group C; $p < 0.001$
12 Months	1.38 - 1.73 - 2.16	0.85 - 1. 17 - 1.47	- 1.50 - 2.01	Group A *vs*. Group B; $p = 0.002$
				Group A *vs*. Group C: $p = 0.450$
				Group B *vs*. Group C; $p = 0.090$
Impairment (%)	+ 132.93	+ 73.40	+ 200.00	Group A *vs*. Group B; $p < 0.001$
				Group A *vs*. Group C; $p = 0.520$
				Group B *vs*. Group C; $p < 0.001$
GROUPS COMPARISONS				
RANKIN	3 Months	12 Months		KRUSKAL-WALLIS TEST:
Group A *vs*. Group B				
Impairment (%)	+ 5.59	+ 33.65		$p < 0.001$ and $p = 0.218$

(Table 1) Contd…

Variable	GROUP A	GROUP B	GROUP C	Differences
Group A *vs*. Group C				
Impairment (%)	+ 77.96	+ 19.58		$p < 0.001$ and $p = 0.172$
Group B *vs*. Group C				
Impairment (%)	+ 33.15	+ 13.25		$p = 0.078$ and $p = 0.106$
CDR				
Group A *vs*. Group B				
Impairment (%)	+ 50.44	+ 48.50		$p = 0.058$ and $p = 0.083$
Group A *vs*. Group C				
Impairment (%)	+ 28.30	+ 15.53		$p = 0.118$ and $p = 0.153$
Group B *vs*. Group C				
Impairment (%)	+ 14.72	- 22.20		$p = 0.098$ and $p = 0.091$

*Age is expressed as mean ± standard deviation. † Results of Rankin and CDR tests are expressed as: lower limit - **mean** - upper limit. Percentage comparisons of differences in the evolution between different groups were calculated as, for example: Percentage = 100 x (Group A - Group B) / (Group B).

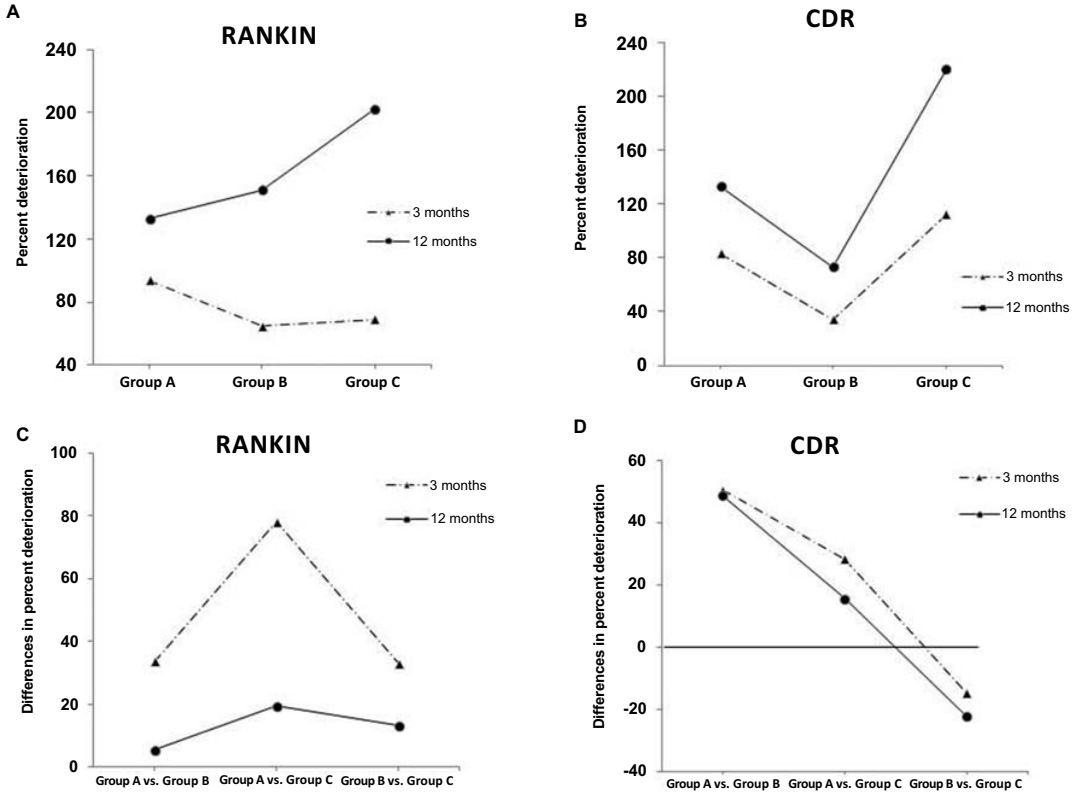

Fig. (2). A and **B:** Comparison of impairment percentages within the groups, **C** and **D**: Comparison of impairment percentages between the groups.

In the lower part of Table **1**, the results of the Kruskal-Wallis statistical test comparing deterioration expressed as percentages of the baseline value of the different groups are presented. In Fig. (**2**), the differences within groups (v.g. their evolution) and the comparison between groups are shown graphically as percent deterioration along the evolution of groups and as differences in percent deterioration at three and twelve months.

In the follow-up, each group showed significant deterioration in DLA and cognition at 3 and 12 months, demonstrated by the highly significant values of the binomial test ($p<<0.001$ for all variables and groups). The greatest deterioration occurred at 3 months in both Rankin and CDR, when compared with baseline values (Fig. **2A** and **B**).

The comparison between groups showed significant differences in Rankin at 3 months, not significant between 3 and 12 months. There were no significant differences in CDR.

The largest difference in Rankin was found in groups A and C, followed by groups B and C (Fig. **2A**); significant differences were found in the comparisons between the three groups (Fig. **2C**). No significant differences were found in the CDR within the groups (Fig. **2B**) and in the comparison between the groups A *vs*. B and A *vs*. C (Fig. **2D**).

4. DISCUSSION

ExL-A is linked to an abnormality of small vessel disease [27], causing a chronic ischemia. L-A lesions are characterized by processes of demyelization, loss of glial cells, venules and precapillary vessels -caused by mutations in collagen 4A1- and being the collagenous thickening of the walls the most often found phenomenon [28]; this pathology is closely associated with hypertension (hypertensive SVD).

The other main type of SVD in ageing is the cerebral amyloidal angiopathy, whose most noticeable features are not as closely related with hypertension. The sporadic cerebral amyloidal angiopathy is a chronic disease with progressive deposition of β- amyloid in the media and adventitia of small arteries [29], and in some cases with associated inflammatory processes.

L-A is frequently encountered in the elderly and is well-known that it contributes to worse outcomes after one episode of acute ischemic stroke. Thus, it is important to understand the potential contribution of L-A to a decrease in activities of Daily Living (DLA) [30, 31].

At the beginning of this century, the LADIS group studied the degree of disability and the worsening of DLA related to the extension of the L-A, and the appearance of stroke, or the addition of silent lacunar lesions [32].

Our working hypothesis requires determining whether ASD and stroke impair differentially DLA and cognition along time in the three groups.

Three months after the stroke (Group A), patients show significantly larger impairment in Rankin than ASD patients (Groups B and C), while 12 months after the event overall impairments are similar between groups. Both types of event, stroke and ASD, determine an immediate impairment of DLA. On the other hand, the progression of the impairment in CDR is similar for the three groups along the study period.

These results suggest that a different mechanism is involved in the deterioration of DLA and cognitive impairment in stroke and ASD. This hypothesis is based on the difference between a focalized injury in the case of stroke, and an impact not directly related with the ExL-A etiology.

Our analysis agree with the reported association of L-A with alterations of equilibrium and falls that worsen the DLA [18, 33]. In many of these patients, the cognitive impairment is not large but contributes, together with motor and sphincter disturbances, to a significant worsening of the DLA.

While the already reported association of stroke and L-A reportedly impairs DLA and cognition [34-38], curiously very few information exists regarding manifestations of L-A and its possible association with ASD, except only in the case of anemia [39]. Results presented here support the hypothesis that general organic ailments influence the development of L-A, reaching an impairment degree similar to that observed in stroke.

This worsening is not associated with deterioration in circulatory conditions, suggesting that larger prospective studies are warranted to validate these outcomes and to investigate the pathophysiological link between leukoaraiosis and acute systemic diseases. These studies might highlight new approaches for diagnosis, monitoring, and treatment. Currently, no new data exist on this issue.

It is important to bear in mind that this study is limited to elderly patients, beyond the life expectancy of the Buenos Aires population from which they were sampled.

CONCLUSION

Briefly, the results of this study are: (I) The worsening of DLA and cognition, present in groups of ASD in hospitalized and ambulatory patients is comparable to the impact of a stroke; (II) The prevalence of the vascular risk factors analyzed was comparable in the three groups, hypertension being the most common risk factor; and (III) In all three groups, impairment produced in Rankin (DLA) is greater than in cognition (CDR) but statistically not significant.

The clinical relevance of this study, at least for these ageing patients, lies on the identification of the need for differential diagnosis in order to achieve the best possible treatment.

CONTRIBUTIONS OF THE COLLABORATORS

Dr. Silvia E. González, M.D: Data collection of patients.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The present protocol was approved by Sirio-Libanes Hospital Ethics Committee.

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The reported experiments on humans were in accordance with the ethical standards of the committee responsible for human experimentation (institutional national), and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/).

CONSENT FOR PUBLICATION

The patients and/or relatives signed an informed consent prior to the incorporation.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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In Memoriam

The present paper is dedicated *in memoriam* to Dr. Eduardo Luis Bartolomé MD, who recently passed away.

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