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ASSOCIATION BETWEEN PAIN AND FATIGUE IN BRAZILIAN PEOPLE WITH MULTIPLE SCLEROSIS: A CROSS-SECTIONAL STUDY

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ABSTRACT

The impact of pain and fatigue on the upper limb (UL) function of people with Multiple Sclerosis (PMS) is well-known, but the relations between them are poorly understood. This study aimed to verify the frequency of the types of pain and the relationship between pain and factors that limit UL function in PMS. This was a descriptive, cross-sectional study. Pain was evaluated by Functional Assessment of Quality of Life in PMS. UL function was evaluated by the hand grip strength and by the *Test d' Evaluation de la performance des Membres Supérieurs des Personnes Âgées (*TEMPA*)*, while the fatigue was evaluated by the Modified Fatigue Impact Scale. Correlations between pain and the other variables were analyzed with the Pearson coefficient. A simple linear regression was used to determine the influence of pain on fatigue. Sample was composed of 32 PMS diagnosed with relapsing remitting type. Muscle pain was the most common type of pain reported by participants (40%). Pain correlated strongly only with fatigue and explained 28% (R^2 = 0.28) of the variance in fatigue scores. This study showed strong association between muscle pain and fatigue (r = - 0.52; p <0.01), and no association between pain and UL function.

Keywords: Demyelination; symptoms; relations.

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INTRODUCTION

Multiple Sclerosis (MS) is a neurodegenerative disorder characterized by the disruption of the myelin sheath in the Central Nervous System (VALENTINE *et al*., 2022). This pathological process arises from an autoimmune dysfunction, leading to the formation of demyelinated lesions in the white matter of the brain and spinal cord (IANNITTI *et al*., 2014).

Development of the disorder is influenced by a combination of genetic and environmental factors (MIRABELLI *et al*., 2021). MS can manifest with various clinical presentations, including isolated syndromes, relapsing-remitting MS, or a primary progressive disease course (OLIVA RAMIREZ *et al*., 2021). Worldwide prevalence of MS is approximately 2.3 million individuals, predominantly affecting young adults between the ages of 20 and 40, with a threefold higher prevalence in women compared to men (MIRABELLI *et al*., 2021). Average prevalence of MS in Brazil is approximately 8.69 per 100,000 inhabitants. However, there is a heterogeneous prevalence distribution across the various geographic regions of the country. For instance, the Northeastern region reports the lowest rate (1.36 per 100,000 inhabitants), while the Southern region exhibits the highest prevalence (27.2 per 100,000 inhabitants). A preliminary study indicates a prevalence rate of 5.85 per 100,000 inhabitants in the Brazilian mid-west region (PEREIRA *et al*., 2015). The heterogeneity in the prevalence of the MS can also be verified in terms of the heterogeneity of its symptoms. People with MS can experience varied symptoms such as spasticity, diplopia, transient or blurred vision, numbness, bladder and bowel dysfunction, sexual dysfunction, upper limb impaired coordination, muscle weakness, fatigue, and pain (IANNITTI *et al*., 2014). The prevalence of pain in people with MS is about 63%. However, as pain in MS data are restricted to studies from Europe and North America, information about pain characteristics in Brazilian MS people is not available (Thomaz *et al.*, 2023). Therapeutic interventions aim to slow the disease progression and alleviate symptoms to enhance the overall quality of life (MIRABELLI *et al*., 2021).

While the isolated impacts of pain and fatigue, on the functionality of people with MS, including upper limb disfunction, are well-known, these health-related problems can remain untreated or undertreated due to both barriers related to knowledge of clinical mechanisms and specific treatment resource (VALENTINE *et al*., 2022), and the limited informations about the relations between these two symptoms. In that way, studying those relations becoming a relevant objective of study. Furthermore, a lack of comprehension regarding the clinical aspects and underlying physiology of pain, contributes to prolonged pain experiences in the patients (SOLARO *et al*., 2018).

Pain affects over 80% of people with MS and the prevalence of chronic pain in this population can increase by almost 15% within the next seven years (KHAN *et al*., 2013; YILMAZER *et al*., 2022). The features of MS-related pain demonstrate that patients experience different types of pain, including neuropathic pain, muscle pain, nociceptive pain, psychogenic pain, idiopathic pain, mixed pain, migraine, and even treatment-induced pain (KHAN *et al*., 2013; HEITMANN *et al*., 2016). In most cases MS-related pain is characterized as mild-to-moderate intensity, episodic, in more than one site, usually in the limbs and with burning sensation. In addition, patients with neuropathic pain can have trigeminal neuralgia (with often bilateral manifestation), optic neuritis and painful Lhermitte's sign associated with painful muscle spasms and allodynia/hyperalgesia. Pain in MS people has also been reported as acute or chronic and it is associated indeed with active inflammatory process. Therefore, the neurodegenerative aspect of MS and the progression of MS-related pain can occur concomitantly with the deterioration of disability (Brown *et al*., 2023; Senders *et al*., 2018).

Recent studies indicate that pain may be related to mood and quality of life impairments, as well as interfering with sleep quality and restriction of occupational and social participation (KHAN *et al*., 2013). According to SOLARO *et al.* (2018) study, pain was more prevalent among females, people with higher EDSS scores, longer disease duration, and older age. Additionally, there was an association between neuropathic pain and EDSS scores. In contrast, the findings by KASAP AND UGURLU (2023) showed that age, sex, marital status, family support, MS subtype, injury location, and disease duration did not exhibit significant associations with pain. Notably, pain was more frequently reported by patients with lower levels of education, pathological fatigue, moderate/severe depression, and reduced quality of life. Moreover, no relationship was observed between EDSS scores and pain, in the same investigation (KASAP AND UGURLU, 2023).

In addition to pain, fatigue is a common disabling symptom of MS and is currently associated with an increase in activity limitations and social participation

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restrictions, reducing the ability to maintain usual activities. Fatigue in MS is characterized by a loss of mental or physical energy to perform daily life activities at home, work, and during leisure activities due to the central or peripheral inflammatory processes (DE HEREDIA-TORRES *et al*., 2020).

Fatigue is an important and frequent symptom in people with MS, being present between 75%-90% of people and described as the worst symptom of the disease by more than 50% of patients. Fatigue is usually perceived as: "lack of energy", "tiredness", "exhaustion", "lack of motivation", "lack of mental or cognitive energy", even for carrying out usual activities.

Besides, the relations between pain and fatigue and how they influence each other, are still poorly known, particularly in Brazilian patients. The statement of a relationship between pain and fatigue could bring new insights for the developing of more effective interventions on pain targeting to minimize fatigue in MS people and, consequently, to improve upper limb disfunction. Therefore, the aim of this study was to verify the frequency of the types of pain and the possible relationship between pain and the factors that can decrease upper limb function in persons with MS, including fatigue.

MATERIALS AND METHODS

Study design

A descriptive, cross-sectional study was performed. The study was approved by the Research Ethics Committee of the Faculty of Ceilândia from University of Brasília, Brazil (opinion number: 4.918.584). All participants were previously instructed on the study procedures, agreed to participate, and signed the Informed Consent, previously to the study beginning.

Sample size

The final sample of the study was obtained by non-probabilistic and convenience sampling during a ten-months patient recruitment period. The study sample comprised 32 patients with MS (7 men and 25 women).

Participants

From July 2022 to May 2023, people diagnosed with MS were invited to participate in the study. Recruitment took place through contact with associations of people with MS and wide dissemination in health services in the Federal District, Brazil.

Participants should have met the following inclusion criteria: a) age $\leq$ 60 and $\geq$ 18 years; b) neurologist-confirmed MS diagnosis according to 2017 McDONALD'S criteria; c) not presenting relapses or exacerbations in the last three months before the beginning of the study; d) accepting and signing the informed consent.

Exclusion criteria were: a) presence of psychiatric diseases; b) presence of other neurological diseases or disorders that could prevent the evaluation procedures.

Procedures

The evaluations were carried out at the Association of People with Multiple Sclerosis of the region. Each participant was evaluated during one visit session that lasted about one hour and a half. Participants were tested by a well-instructed and trained occupational therapist. The order of application of the assessment instruments was randomized for each patient. Participants previously completed a demographic and clinical questionnaire.

Pain symptoms (Independent Variable)

Pain symptoms were registered based on the symptoms´ domain of the Functional Assessment of Quality of Life in Patients with MS (FAMS). This instrument was validated for the Brazilian population (MENDES *et al*., 2004). FAMS is composed of six domains: mobility, symptoms, emotional state, personal satisfaction, thinking and fatigue, social and family situation. All domains have seven items that allow scores from 0 to 28 for each domain, except for thinking and fatigue domain, which has nine items, with their scores ranging from 0 to 36. The format of the responses, on a Likert scale, allows scores from 0 to 4 for each item. Scores of negatively worded statements are reversed and, therefore, a high score means good quality of life.

Of the 53 items, 44 of them are used to obtain the total score. The remaining nine items in the appended domain (allowing a total score of 36 points) are presented as they provide relevant clinical and social information, however, they should not be used to obtain the final score. FAMS ranges from 0 to 176 points. After validation for the Portuguese language, the questionnaire maintained the characteristics of the one originally described in terms of

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internal consistency, reliability, and sensitivity, and can be used in clinical practice and clinical trials.

FAMS symptoms domain is composed by four questions about pain in which information on general pain, joint pain, headache, and muscle pain are requested. Total score of pain subscale ranges from 0 to 16 and was established by the sum of the scores of the four answers on pain. In this case, the higher scores, the lower the reported pain. Advantages for using FAMS symptoms domain as pain evaluation are due the fact that there are no specific scales for pain evaluation in MS, being FAMS more sensitive and FAMS is able to determine the most common pain type in a sample.

Upper limb´s Function (Dependent Variables)

For the upper limb`s function evaluation, two tests were used.

Hand grip strength: to perform the test, using a hydraulic hand dynamometer SH5001 by Saehan©, the patient should be seated in a chair with a straight back and without support for the arms, the shoulder adducted and neutrally rotated, elbow flexed at 90º, forearm in neutral position and wrist between 0º and 30º of extension and 0º and 15º of ulnar deviation. The test was applied three times, and the registered value was the highest among the three attempts (CUESTA-VARGAS *et al*., 2015; REIS & ARANTES, 2011).

Testd' Evaluation de la performance des Membres Supérieurs des Personnes Âgées (TEMPA) is a tool for evaluation of upper limb daily functionality. It is validated for people with MS, and the Brazilian version consists of eight standardized tasks that simulate everyday activities. It is performed in two stages: unilateral and bilateral (FEYS *et al*., 2002). Unilateral activities were represented by picking up and carrying a pot, picking up a pitcher and pouring water into a glass, handling coins, and picking up and moving small objects. The bilateral ones consist of opening a pot and taking a spoon full of coffee, unlocking the lock and opening a container containing pills, writing on an envelope and sticking a stamp and shuffling and distributing playing cards (DE FREITAS *et al*., 2017). The participant´s performance is based on the time spent to complete each task. Advantages for using TEMPA as upper limb daily functionality evaluation are due the fact that it evaluates upper limb function in real motor daily tasks, in real contexts, using real daily materials, increasing, therefor, the ecological validity of this assessment.

Perceived fatigue was evaluated by the Modified Fatigue Impact Scale (MFIS). Adapted to Brazilian individuals and validated for the population with multiple sclerosis, this test has 21 items and determines the effects of fatigue on cognitive (10 items), physical (9 items) and psychosocial (2 items) factors (PAVAN *et al*., 2007). The cognitive domain spans from 0 to 40 points, the physical, from 0 to 36 and the psychosocial from 0 to 8, in which the patients are asked to rate on a 5-point Liker scale if fatigue has caused problems for them during the previous month. The total score is given by the sum of the partial scores, ranging from 0 to 84, where higher scores mean higher level of fatigue. This questionnaire has obtained good test–retest reliability and validity in MS.

Statistical analysis

Statistical analyses were processed using the Statistical Package for Social Science software version 22.0. Continuous data were analyzed descriptively, using measures of central tendency (mean or median) and variability (standard deviation or interquartile range 25-75), and categorical data were presented in percentage and absolute frequency. The Kolmogorov-Smirnov test was used to verify the data distribution.

The correlations between pain and the other variables were analyzed, with the Pearson coefficient, calculated considering the 95% confidence interval. According to COHEN (1988), values can be interpreted as: between 0.10 and 0.29 can be considered small (weak correlation); scores between 0.30 and 0.49 can be considered average (moderate correlation); and values between 0.50 and 1 can be interpreted as large (strong correlation). Since fatigue was the only outcome that reached a significant and strong statistical correlation with pain, a simple linear regression was used to determine the influence degree of pain on fatigue.

RESULTS

Table 1 displays the general characteristics of the sample. In total, sample was composed in the most part for female participants, with the relapsing remitting type of MS, high level of education, full ambulation, and moderate disability, and with intermediate perception of pain and fatigue.

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Table 1. General sample´s characteristics (N=32).

Variables	Mean	SD
Age (y)	38.69	10.97
Education (y)	15.81	2.84
EDSS (score)	3.34	1.31
Duration of disease (y)	5.91	3.61
Number of relapses	4.31	2.96
Hand Grip Strength (N/m)	24.54	7.42
Tempa total (sec.)	230.54	52.09
MFIS total (Score 0-84)	48.88	10.37
FAMS total (Score 0-176)	96.09	16.95
Total Pain (Score 0-16)	8.53	4.15
	N (%)	
Sex (female)	25 (75.83)	
MS type		
Relapsing Remitting	26 (78.85)	
Primary Progressive	4 (12.1)	
Secondary Progression	2 (6.10)	

Legend: SD, Standard Deviation; y, years; N/m, Newtons/meter; EDSS, Expanded Disability Status Scale; sec., seconds; TEMPA, *Testd' Evaluation de la performance des Membres Supérieurs des Personnes Âgées*; MFIS, Modified Fatigue Impact Scale; FAMS, Functional Assessment of Quality of Life in Patients with MS.

Table 2 shows the frequencies of the types of pain into the sample. It is possible to verify that muscle pain was the most common type of pain reported by the participants.

Table 2. Absolute and relative frequencies of the types of pain into the sample.

Types of pain	N (%)
General pain	7 (21)
Joint pain	5 (15)
Headache	7 (21)
Muscle pain	13 (40)

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Table 3 shows correlations between pain and other study variables. No variable but total MFIS showed a significant association with pain. Considering the score´s characteristics of the pain and fatigue scales, those variables exhibited a strong inverse correlation (R = -0.52). However, the relationship between the variables must be understood how higher levels of pain are associated with higher levels of fatigue (p=0.001). FAMS was not tested for pain correlation since pain outcome is a FAMS subscale.

Table 3. Correlations between Pain and other variables.

	Pain	
	r	*p*
Age	-.13	.47
Education	-.05	.78
EDSS	-.15	.38
Duration of disease	-.00	.98
Number of relapses	-.19	.27
Hand Grip Strength	.23	.19
Tempa	.14	.42
Total MFIS	-.52	<0.01

Legend: r, Pearson´s correlations; EDSS, Expanded Disability Status Scale; TEMPA, *Testd' Evaluation de la performance des Membres Supérieurs des Personnes Âgées*; MFIS, Modified Fatigue Impact Scale.

Simple linear regression was performed to determine if pain significantly would predict the perceived fatigue. The overall model was significant (F (1,30) = 11.67, p=0.002) for pain, explaining 28% (R2 = 0.28) of the variance in fatigue scores, suggesting that patients with high levels of pain had also, greater fatigue (Table 4).

Table 4. Simple linear regression with MFIS as dependent variable.

	Pain		
	β(SE)	t	p value
MFIS	- 1.32 (0.38)	-3.41	0.00
R	-0.52		
R^2 (%)	0.28		
Model	F (1.30) = 11.67, p=0.00		

Legend: SE, Standard Error; MFIS, Modified Fatigue Impact Scale.

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DISCUSSION

To the best of knowledge of the authors, this is the first study aiming to verify the possible relationship between pain symptoms and other variables that could decrease functionality in people with MS, in a Brazilian sample. To do this, thirty-two people with MS were evaluated in pain, upper limb function, fatigue, and quality of life tests. The main results showed that pain is associated with fatigue but not with other variables.

Pain is one of the most frequently reported symptoms of MS, and it affects the activities of daily living of patients, limits the ability to work and reduces the quality of life, beyond to cause symptoms of anxiety and depression (STENAGER *et al*., 1995).

Previous studies showed that pain symptoms were associated to several motors and non-motors conditions in people with MS. LABUZ-ROSZAK *et al.* (2019) studied 144 patients with MS (age 41±12 years, mean illness duration 10.3±8.6 years), who were evaluated on current and previous pain symptoms by means of the Quality-of-Life self-esteem Questionnaire (EQ-5D) and by the Hospital Anxiety and Depression Scale (HADS). It was observed an association between presence of pain and gender ($p< 0.01$), age ($p< 0.05$), the degree of disability ($p< 0.05$), education ($p< 0.001$), and the professional activity ($p< 0.01$); Authors concluded that female gender, advanced age, reduced functional capacity and lower education, can predispose the occurrence of pain in patients with MS.

Other studies showed evidence of the negative impact of the presence of pain on the quality of life and activities of daily living, in MS patients who had predisposition to develop pain during the course of the disease (FERRARO *et al*., 2018).

However, in the present study, no associations were found between pain and age, education, ambulation capacity, duration of disease, number of relapses, force, and upper limb (UL) functionality, although pain has been associated with perceived fatigue. Missing associations, mainly, between pain and force and between pain and UL functionality were intriguing, considering the theoretical link among these variables. Although the choice of FAMS as pain assessment has been done by its possible bigger sensitivity in people with MS, since there are no specific pain scales for that population, it contains only four questions about pain, and it could bring few detailed information on it. This could explains the missing relations founded.

KASAP AND UGURLU (2023) observed association between pain and low education level (less than 10 years of formal education), with the presence of pain symptoms being more common in subjects with a low educational level. In the present study, however, no relationship was found between pain and education. It should be noted that in our sample, there were no individuals with less than 10 years of schooling, and this could explain the missing association between them. Therefore, our convenience sampling prevented a bigger range of education levels among the participants, and it should be considered with caution in terms of generalization of these results. This result, on the other hand, was consistent with another study carried out in the population of Saudi Arabia, where 98.3% of the sample had more than 10 years of schooling, and no relationship was found with pain (AMER *et al*., 2022).

Da Silva *et al*., investigated the presence of pain among MS patients, who responded questionnaires evaluating neuropathic and nociceptive pain, depression and anxiety. Authors observed that women had a statistically higher prevalence of pain and reduced chance of having pain after the age of 50 years, and pain had a statistically significant inverse relation with the number of relapses: after the second relapse, each relapse reduced the chance of having pain by 46%. The presence of pain was independent of EDSS, anxiety, and depression, and indicated a possible protective role of focal inflammation in the control of pain. In women, by the action of gonadotropin-releasing hormone, it seems to be indicative of female-related hormones/genes causing an increase in relapses and their surrogate lesions as a possible "protective" function reducing pain-related brain activation in anticipation (SILVA *et al*., 2015). This could be a possible explanation for the fact that we did not find an association between pain and relapses in this sample, since it was made up of 75% of women, despite other studies available in the literature pointing to associations of these events with the presence of pain symptoms (LABUZ-ROSZAK *et al*., 2019). Comparative studies between groups considering gender, clinical course of disease and pain, could be useful to clarify this question, but unfortunately those were not objectives of the current study. We also considered that our sample, constituted mainly for women, prevented deeper analysis about gender influences on pain aspects due to the impossibility of subdivide the sample in gender comparable groups.

Regarding the types of pain frequently present in individuals with MS, muscle pain was observed as the

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most prevalent (40% of the sample), followed by general pain and headache (both 21%) and lastly (15% of joint pain). KAHRAMAN *et al.* (2019). verified the frequency and types of pain in individuals with MS using the Nordic symptoms questionnaire, with musculoskeletal pain being the most frequent, similarly to our study, representing 55.6%, followed by neuropathic pain with 21%. Although our study has used a different tool for pain assessment (FAMS), it was noted that the frequency was similar, with muscle pain being the most common, whereas the cross-sectional study carried out by AMER *et al.* (2022) concluded that 1 in 3 people with multiple sclerosis complain of muscle pain associated with high disability, and the other two thirds have muscle pain with little impact on functional capacity.

Thus, it can be observed that despite the different forms of evaluation and classification, muscle pain seems to be the most frequent in people with MS. In the two studies cited there was no headache as a complaint.

On the other hand, BECKMAN AND TURE (2019) investigated the prevalence and characteristics of headaches in MS subjects and it occurred in 68% of cases and probably these results indicate that a possible relationship may exist between headache and MS medication, since 80% of patients described headaches after the onset of treatments.

Although the literature establishes the influence of pain on functional capacity in people with MS, especially in manual dexterity (O'CONNOR *et al*., 2008), in this study, no statistically significant associations were found between EDSS, handgrip test and TEMPA upper limb performance and pain.

VELIČKAITĖ *et al*. (2020) found a moderate and positive relationship between pain and levels of disability measured through the EDSS, and those who had higher scores on pain levels also had higher scores on the EDSS. However, this result was achieved when the sample was divided by sex, being the result found exclusively for males (TRUINI *et al*., 2012).

In the current study, however, was not possible to compare groups by gender, but it is a consensus in the literature that male sex is independently associated with faster disability, achieves higher scores on the EDSS over a period of time shorter when compared to women; the same phenomenon does not happen when the group becomes homogeneous (men and women) (RIBBONS *et al*., 2015).

All our participants reported fatigue. The prevalence of fatigue described in people with MS is high, ranging from 60% to 95%, and is often associated with worse quality of life and absenteeism in work activities (TROJAN *et al*., 2007).

In this study, pain showed a strong correlation with fatigue and this finding is in line with previous studies (BECKMAN AND TURE, 2019; HEITMANN *et al*., 2022). Additionally, it was observed in a longitudinal study that this relationship becomes stronger over time suggesting the same pathophysiological mechanism to explain pain and fatigue (HEITMANN *et al*., 2020). In fact, pain and fatigue seem co-occur in prodromal phase and in early MS, suggesting a common etiology. Besides, neuroimaging studies have shown overlapping of structural and functional alterations of mesocorticolimbic pathways in patients who present pain and fatigue and both symptoms have been linked to dysfunction of monoaminergic neurotransmission in central nervous system inflammation (HEITMANN *et al*., 2022).

The explanatory model of linear regression indicated that pain explained 28% of the fatigue variability. Considering the same pathophysiological mechanism and influence of pain on fatigue, we could infer that therapeutic interventions focused on pain may contribute to decrease fatigue. Since fatigue is a symptom that is more complex to therapeutically cope and brings a negative effect on quality of life, possibly would be more efficient to treat pain in order to minimize fatigue in people with MS.

As strengths of the present study, it is worth highlighting that the instrument used to assess quality of life and extract information about pain was specific for subjects with MS. As limitations, once this was a cross-sectional study, it was not possible to understand the behavior of symptoms such as pain, fatigue and upper limbs disfunction over time, to assess how they evolve. Another important limitation was the lack of control in terms medication use, since some drugs could influence in participants´ pain perception. Therefore, a cohort study, including longitudinal data and drugs use control could be useful in future studies to understand these inconsistencies present in literature, and using specific instruments for the population with MS. Additionally, the small sample size is another limitation of this study. Considering the huge MS population´s clinical heterogeneity, the founded results cannot be generalized for all possible clinical types of MS.

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CONCLUSIONS

This study showed that the most common pain type found in a Brazilian sample of people with MS was muscle pain. It was also found that there were no relations between pain and age, education level, disease stage and duration, number of relapses, hand grip strength or upper limbs function. However, it was found strong association between pain and fatigue. Therapeutic interventions such drug or physical therapies focused in muscle pain could minimize fatigue effects in this population.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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