

Original Article

Neuropathic Pain Component in Patients with Ankylosing Spondylitis and the Relationship of Neuropathic Pain and Disease Activity Parameters: A Cross-Sectional Study

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Abstract

Objective: It is known that neuropathic pain frequently accompanies rheumatological diseases. In this study, neuropathic pain in Ankylosing Spondylitis(AS) and its relationship with disease activity were investigated. **Methods:** Forty patients with AS were included. Laboratory data and disease status parameters were recorded. Neuropathic pain questionnaires were administered. Electrophysiological examination was performed on all patients. The relationship between neuropathic pain and disease activity parameters was investigated. **Results:** According to the Pain Detect and LANSS questionnaire results, the rate of neuropathic pain was 57.5% and 42.5%. ASQoL, BASDAI, and ASDAS-ESH parameters are statistically significantly higher in the group with neuropathic pain according to the PainDetect (p:0.018, p:0.04, p:0.028). MASES, ASQoL, BASDAI, BASFI, and ASDAS-ESH parameters are statistically significantly higher in the group with neuropathic pain according to the LANSS (p:0.004, p:0.005, p: 0.001, p:0.005, p:0.02). Disease activity is higher in patients with neuropathic pain for both scales. Peripheral neuropathy is detected in nine patients. There is a positive correlation between disease activity parameters and neuropathic pain scales. A strong positive correlation was detected between ASQoL and BASDAI parameters and the Pain Detect questionnaire (r:0.533, r:0.606). **Conclusions:** The majority of patients with AS have a neuropathic pain. This condition is associated with high disease activity and adversely affects the patient's quality of life.

Keywords: Ankylosing Spondylitis, Electrophysiology, Neuropathic Pain, Quality of Life, The Disease Activity

Introduction

Spondyloarthritis (SpA) is a heterogeneous group of chronic autoimmune diseases with common genetic predisposition and similar clinical and radiological features, with a reported prevalence of 0.5-1.5%¹.

Patients diagnosed with ankylosing spondylitis(AS) constitute the majority of the SpA group. AS patients

present with chronic low back pain. Many studies have shown that 16 to 54% of patients with chronic low back pain have a neuropathic pain component. While neuropathy has been shown in rheumatoid arthritis, osteoarthritis, and fibromyalgia so far, there are not many studies on this subject in AS². Pain in AS is typically of nociceptive origin but the presence of symptoms and findings such as burning sensation, hyperalgesia, and allodynia in AS patients cannot be adequately explained by nociceptive pain.

In recent years, data on early diagnosis and effective treatment options in AS have been increasing. Although many clinical and experimental studies have been conducted on AS, pain control in patients with AS is difficult. Current biologic or conventional treatments result in reduced inflammation in skeletal sites. However, some patients with AS cannot provide complete pain control. Some AS patients with neuropathic pain components are

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relatively resistant to treatments³.

There are some discrepancies between the degree of inflammation and the severity of pain. Wu et al. showed that low back pain contains a neuropathic pain component in more than half of patients with AS³. Having neuropathic pain is also associated with low quality of life, high pain scores, and high disease activity scores. There have been several studies investigating the neuropathic pain component and its relationship with disease activity in patients with AS⁴.

Subclinical peripheral neuropathy in rheumatological diseases such as rheumatoid arthritis and Behçet's disease has been evaluated by nerve conduction studies^{5,6}. However, there are limited studies evaluating peripheral neuropathy in patients with AS. In a study, a neurophysiological examination was performed on 24 patients with AS, and neurophysiological abnormalities were found in approximately 70.8% of the patients⁷. It was thought that detecting a subclinical peripheral neuropathy that may exist in the background by performing nerve conduction studies in the group without complaints may be beneficial in terms of early diagnosis and treatment.

Therefore, in our study, we aimed to evaluate the neuropathic pain component by LANSS and Pain Detect questionnaires and nerve conduction study findings in patients with AS. In addition, our second aim is to investigate the relationship between disease activity parameters and neuropathic pain scores.

Materials And Methods

Forty people were included in this study. Between September 2019 and January 2020, 40 people who were diagnosed with AS according to 1984 Modified New York Criteria⁸ and ASAS-2010⁹ criteria, who applied to the Rheumatology Outpatients Clinic of University Hospital, were included. Patients with diabetes mellitus, hypothyroidism, amyloidosis, alcohol intake, liver and kidney failure, pregnancy, hereditary neurological disease, vitamin D or vitamin B12 deficiency, fibromyalgia, and radicular pain were excluded. The sample size was calculated on the basis of the significant statistical findings obtained by previous studies^{3,4,10}. It was decided to include 40 individuals in the study. The alpha level was set at 0.05 with a power of 80%.

Demographic and clinical data of the patients such as age, gender, educational status, comorbidities, duration of disease, extra-articular involvement, peripheral involvement, drugs, results of ESR, CRP, and HLA-B27 were recorded.

Bath AS Disease Activity Index (BASDAI), AS Disease Activity Score (ASDAS), The Bath AS Functional Index (BASFI), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and Bath Ankylosing Spondylitis Metrology Index (BASMI) were evaluated to determine the disease activity and its effect on the musculoskeletal system, functional status and quality of life by the same physician (SA).

BASDAI and ASDAS indices were used to evaluate the disease activity of the AS patient group^{11,12}. Four or more

are considered active diseases¹³. The ASDAS consists of four questions that patients will answer and CRP or ESR values. The results are analyzed in four groups. If the score is <1.3, it is inactive disease, if the score is ≥ 1.3 –<2.1, it is low disease activity, if the score is ≥ 2.1 – ≤ 3.5 , it is high disease activity, and if the score is >3.5, it is very high disease activity. The higher this value, the higher the severity of disease activation¹⁴.

The BASMI index was used to evaluate spinal mobility¹⁵. Tragus-wall distance, lumbar flexion, cervical rotation, lumbar lateral flexion, and intermalleolar distance of the patients were measured in centimeters. The total score obtained by the patients was calculated and recorded.

The MASES index was used to determine the sensitivity of the enthesitis points with palpation in the AS patient group¹⁶. BASFI was used to evaluate the functional status of the patients¹⁷. The Turkish version of the ASQoL questionnaire was used to assess the quality of life in AS patients. ASQoL is an AS-specific quality of life scale consisting of 18 questions with two-choice (yes-no) answers. The maximum score is 18, and the score is inversely proportional to the quality of life¹⁸. Pain Detect, which includes only a questionnaire, and LANSS questionnaires, which include sensory examination in addition to the questionnaire were administered to determine the presence of neuropathic pain by the same investigator (SA). Turkish validity and reliability of both scales have been demonstrated¹⁹. LANSS consists of 7 items in total. Five of these include questions questioning pain symptoms. The other two are for sensory examination including allodynia and pinsense test. The scale is scored between 0–24, a score of 12 and above suggests neuropathic pain²⁰. The Pain Detect questionnaire was developed in Germany specifically to assess low back pain. It is a patient-based questionnaire consisting of 7 weighted sensory descriptive items and two items related to the extent and time of the patient's pain. It can be said that the probability of neuropathic pain is above 90% for those who score above 19. In those with scores between 12–19, the result is uncertain¹⁸. In our study, a score of 13 and above was accepted as neuropathic pain.

Electrophysiological examination was performed to objectively evaluate peripheral neuropathy with a Micromed electroneuromyography device and System Plus Evolution software. Electrophysiological examination was performed using the Micromed brand (Micromed Group, Mogliano Veneto, Italy). During the examination, the room temperature was kept at 22–24°C and the extremity temperature was kept at 34°C. The extremity was warmed when necessary. Two motors and two sensory nerves (median and ulnar nerves) in both upper extremities, two motors (tibial and peroneal nerves), and one sensory (sural nerve) nerve conduction study in both lower extremities were performed. The orthodromic method was used for sensory nerve conduction, and the antidromic method was used only for the sural nerve. Supramaximal stimulation was given for optimal response in all nerve conduction studies. F responses were obtained from the ipsilateral extremities where nerve conduction was recorded. Ten maximal stimuli were given at a frequency of 0.5 Hz and

Table 1. Clinical and Demographic Data of AS Patients.

Age, mean (SD)	42.17 (10.27)
Gender, Female, n (%)	21 (57.5%)
Involvement type, n (%)	
Axial	30 (75%)
Axial+peripheral	10 (35%)
Diagnosis time, year, median (min-max)	5 (1-39)
Drugs used, n (%)	
NSAID	3 (7.5%)
Salazopyrin	3 (7.5%)
Biologic drug	34 (85%)
CRP, mean (SD)	5.96 (5.22)
Sedimentation, mean (SD)	13.55 (7.4)
HLA B27, positive, n (%)	36 (90%)
BASDAI, mean (SD)	5.43±2.42
BASMI, mean (SD)	4.32±1.59
BASFI, mean (SD)	4.95±2.27
ASDAS-CRP, mean (SD)	2.85±0.99
ASDAS-ESH, mean (SD)	2.82±0.96
ASQoL, median (min-max)	12 (0-18)
MASES, mean (SD)	4.32±3.22
PainDetect, median (min-max)	15 (1-24)
LANSS pain scale, median (min-max)	8.5 (0-21)

CRP: C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C reactive Protein, ASDAS-ESH: Ankylosing Spondylitis Disease Activity Score-Erythrocyte Sedimentation Rate, ASQoL: Ankylosing Spondylitis Quality of Life, MASES: Maastricht Ankylosing Spondylitis Enthesis Score.

a duration of 0.2 ms from the wrist and ankle. Responses less than twenty μ V were considered as true F responses²¹. Axonal pathology and demyelination in nerves; It was defined as a decrease in sensory and mixed nerve action potential amplitude or a slowdown in the conduction speed of sensory/motor nerves. For normal values, normal nerve conduction data determined by Shin J. OH at the Electromyography Laboratory of the University of Alabama at Birmingham in May 1983 were used²².

Statistical Analysis

Statistical analysis of study data was performed using Statistical Package for Social Sciences (SPSS) version 22.0. The conformity of the quantitative data to the normal distribution was examined using the Shapiro-Wilk test. Descriptive statistics of the data were given

as mean±standard deviation and median (min-max). For quantitative data suitable for normal distribution, analyses were performed using Student's t-test in independent groups according to the number of groups. For quantitative data not suitable for normal distribution, analyses were performed using the Mann-Whitney U. The relationship between the data in the patient group was analyzed by Pearson Correlation for data with normal distribution, and Spearman Correlation test for data not suitable for normal distribution. The α error level was taken as 0.05.

Results

Of the 40 AS patients who participated in the study, 21 (57.5%) were female and 19 were male. The mean age of the patients is 42.17±10.27 years. Demographic and clinical data of AS patients are summarized in Table 1.

Neuropathic pain is detected in 23 (57.5%) AS patients according to the PainDetect questionnaire and in 17 (42.5%) according to the LANSS questionnaire. The presence of neuropathic pain is similar between genders ($p=0.093$). Participants with neuropathic pain have longer symptom duration than AS patients without neuropathic pain. ($p=0.007$).

Nerve conduction studies are abnormal in 9 patients (Table 2). One of these patients has cubital tunnel syndrome, the other eight patients have carpal tunnel syndrome.

According to the Pain Detect questionnaire results, ASQoL was found to be 10(2-15), BASDAI 4.17±2.23, ASDAS-ESH 2.43±0.87 in the group without neuropathic pain, and 13(0-18), 6.35±2.16, 3.10±0.94, respectively, in the group with neuropathic pain. ASQoL, BASDAI, and ASDAS-ESH parameters are statistically significantly higher in the group with neuropathic pain ($p=0.018$, $p=0.04$, $p=0.028$) (Table 3). According to the LANSS questionnaire results, MASES was found to be 3(0-13), ASQoL 10(0-15), BASDAI 4.24±2.17, BASFI 4.11±2.25, ASDAS-ESH 2.43±0.86 in the group without neuropathic pain, and 7(0-11), 14(1-18), 7.03±1.74, 6.09±1.80, 3.34±0.85 respectively, in the group with neuropathic pain. MASES, ASQoL, BASDAI, BASFI, and ASDAS-ESH parameters are statistically significantly higher in the group with neuropathic pain according to the LANSS questionnaire ($p=0.004$, $p=0.005$, $p=0.001$, $p=0.005$, $p=0.02$) (Table 4). In addition, regardless of the scales, the rate of neuropathic pain is higher in patients with high or very high disease activity than in patients with low and very low disease activity ($p=0.008$ and $p=0.003$).

A positive and statistically significant correlation is found between both neuropathic pain measures and all scales except BASMI (between $r=0.27$ to $r=0.6$) (Table 5).

Discussion

In our study, the presence of neuropathic pain components in 40 AS patients with questionnaires and the presence of peripheral neuropathy with peripheral nerve conduction

Table 2. Distribution of neuropathic pain according to nerve conduction.

Nerve Conduction Study	According to PainDetect		According to LANSS	
	Patients with Neuropathic Pain (n=23)	Patients without Neuropathic Pain (n=17)	Patients with Neuropathic Pain (n=17)	Patients without Neuropathic Pain (n=23)
Normal, n (%)	15 (65.2)	16 (94.1)	11 (64.7)	20 (86.9)
Peripheral Neuropathy n(%)	8 (34.7)	1 (5.9)	6 (35.2)	3 (13.1)

Table 3. Comparison of disease activity parameters and laboratory findings of AS patients with and without neuropathic pain according to the PainDetect questionnaire.

	PainDetect		p
	Neuropathic Pain (-) (n=17)	Neuropathic Pain (+) (n=23)	
MASES ^a	3 (0-13)	5 (0-11)	0.052
ASQoL ^a	10 (2-15)	13 (0-18)	0.018*
BASMI ^a	4 (1-8)	4 (3-6)	0.614
BASDAI ^b	4.17±2.23	6.35±2.16	0.04*
BASFI ^b	4.22±2.45	5.49±2.02	0.083
ASDAS-ESH ^b	2.43±0.87	3.10±0.94	0.028*
Patients with high or very high disease activity ^c	2 (11.7)	21 (91.3)	0.008*

MASES: Maastricht Ankylosing Spondylitis Enthesis Score, ASQoL: Ankylosing Spondylitis Quality of Life, BASMI: Bath Ankylosing Spondylitis Metrology Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASDAS-ESH: Ankylosing Spondylitis Disease Activity Score-Erythrocyte Sedimentation Rate. ^a Values are given as median (min-max). ^b Values are given as mean±standard deviation. ^c Values are given as n (%). ***p<0.05 statistically significant**. p values were calculated by Mann-Whitney U (non-normally distributed variables) and Student T-test (normally distributed variables).

Table 4. Comparison of disease activity parameters and laboratory findings of AS patients with and without neuropathic pain according to LANSS questionnaire results. Values are given as mean±standard deviation.

	LANSS		p
	Neuropathic Pain (-) (n=23)	Neuropathic Pain (+) (n=17)	
MASES ^a	3 (0-13)	7 (0-11)	0.004*
ASQoL ^a	10 (0-15)	14 (1-18)	0.005*
BASMI ^a	4 (1-8)	4 (3-6)	0.341
BASDAI ^b	4.24±2.17	7.03±1.74	0.001*
BASFI ^b	4.11±2.25	6.09±1.80	0.005*
ASDAS-ESH ^b	2.43±0.86	3.34±0.85	0.02*
Patients with high or very high disease activity ^c	0 (0)	10 (58.8)	0.003*

MASES: Maastricht Ankylosing Spondylitis Enthesis Score, ASQoL: Ankylosing Spondylitis Quality of Life, BASMI: Bath Ankylosing Spondylitis Metrology Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASDAS-ESH: Ankylosing Spondylitis Disease Activity Score-Erythrocyte Sedimentation Rate. ^a Values are given as median (min-max). ^b Values are given as mean±standard deviation. ^c Values are given as n (%). ***p<0.05 statistically significant**. p values were calculated by Mann-Whitney U (non-normally distributed variables) and Student T-test (normally distributed variables).

Table 5. The relationship between the results of neuropathic pain assessment questionnaires and AS disease parameters.

Neuropathic Pain Questionnaires	ASQoL	MASES	BASFI	BASDAI	BASMI	ASDAS-ESH
PainDetect	r: 0.533**	r: 0.474*	r: 0.449*	r: 0.606**	r:0.12	r: 0.483*
LANSS	r: 0.418*	r: 0.398*	r: 0.379*	r: 0.503*	r:0.125	r: 0.453*

*MASES: Maastricht Ankylosing Spondylitis Enthesis Score, ASQoL: Ankilozan Spondilit Quality of Life, BASMI: Bath Ankylosing Spondylitis Metrology Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASDAS-ESH: Ankylosing Spondylitis Disease Activity Score-Erythrocyte Sedimentation Rate. *p<0.05. **p<0.001. The relationship between ASQoL, MASES, BASMI parameters and neuropathic pain was evaluated by Spearman, and the others by Pearson correlation analysis.*

studies were evaluated, and possible relationships between these findings and disease parameters were investigated.

Although many clinical and experimental studies have been conducted on AS, pain control in patients with AS is still very difficult. The presence of neuropathic pain-like symptoms such as burning sensation, hyperalgesia, and allodynia in patients with AS cannot be adequately explained by nociceptive pain. Inflammation plays a key role in the formation of pain. However, studies are showing that persistent pain persists despite the suppression of inflammation, thus suggesting that other factors play a role in the perception of pain²³. Recent studies have focused on the neuropathic component of pain in AS patients²⁴⁻²⁶.

In our study, we found that 67.5% of AS patients according to the PainDetect questionnaire results, and 42.5% of the patients according to the LANSS questionnaire results have a neuropathic pain component. Among the studies that included patients with a score of 19 and above in the neuropathic pain group according to the PainDetect survey results, Garip et al.²⁵ found 28% of AS patients Mesci et al.¹⁰ in 30% of AS patients, and Geler-Külcü et al.²⁶ reported that 14% of AS patients had neuropathic pain. Wu et al.³ on the other hand, accepted 13 points and above as neuropathic pain according to the PainDetect survey results in their study and showed that 11 (64.7%) of 17 AS patients had neuropathic pain. The results of our study were also similar to those of Wu et al. This difference between studies is because the patients in the first 3 studies were included in the group with definite neuropathic pain according to the PainDetect questionnaire results, and the patients in these 3 studies had lower BASDAI values (BASDAI <4) than the study by Wu et al. and the patients included in our study. We think it's because of it.

Although nociceptive pain occurs due to inflammatory processes at the beginning of the disease, as the disease becomes chronic, the neuropathic pain component may accompany nociceptive pain through peripheral and central sensitization mechanisms. Cytokines in the inflammatory cascade may play a role in maintaining chronic pain and central sensitization²⁷. Pain occurs with an increase in prostaglandin and bradykinin levels in the synovium due to inflammation and stimulation of unmyelinated C fibers²⁸. Inflammation occurring in the spine, entheses, and synovium

may cause pain by affecting the peripheral nervous system²⁵. In these patients, nerve compression caused by arthritis or tenosynovitis, amyloidosis, autoimmunity, and the side effects of the drugs used may cause peripheral nerve involvement²⁹.

In our study, in AS patients with neuropathic pain according to the PainDetect and LANSS questionnaire ASQoL, BASDAI, and ASDAS-ESH were statistically significantly higher. Similar to our study, in the study of Gök et al., BASDAI, BASFI, and ASQoL scores were found to be statistically significantly higher in the group with neuropathic pain compared to the other group⁴. This situation requires considering the presence of neuropathic pain components when the pain cannot be controlled in cases where the objective parameters of inflammation such as ESR and CRP are low. In the study of Choi et al., BASDAI, peripheral arthritis, and enthesitis scores were found to be statistically significantly higher in the neuropathic pain group compared to the group without neuropathic pain²⁴. In the study of Külcü et al., BASDAI, ASDAS-CRP, ASDAS-ESH, and BASFI values were found to be statistically significantly higher in AS patients with neuropathic pain compared to AS patients without neuropathic pain²⁶. In a meta-analysis including neuropathic pain studies in AS patients, it was concluded that patients with neuropathic pain had higher pain severity and disease activity scores and lower quality of life compared to patients without a neuropathic pain component². In our study, similar results were obtained from the studies in the literature.

Although there are many studies in the literature investigating peripheral neuropathy electrophysiologically in RA patients³⁰⁻³⁵. We found a limited number of studies in AS patients^{36,37}. Erdal et al. found neuropathic pain symptoms in 62% of patients with As. In electrophysiological examination, they found peripheral neuropathy in 17 patients. In this study, it was reported that peripheral neuropathy may be seen more frequently in AS patients than in the normal population and that clinical peripheral neuropathy assessment and use of LANSS in patients with neuropathic pain can be used for appropriate treatment and early diagnosis³⁷. In the study of Gündüz et al., the findings of nerve conduction studies were evaluated in patients with AS. In this study, findings consistent with peripheral nervous system involvement in 18.8% of

patients and focal nerve involvement in 21.9% of patients were obtained. As a result of this study, it was stated that the peripheral nervous system as well as the central nervous system could be involved in AS patients³⁶. In our study, entrapment neuropathy was detected in 9 (22.5%) of the patients participating in the study. Our results were similar to those of Gündüz et al. According to these results, we can say that AS disease may cause a greater predisposition to peripheral nerve lesions.

In our study, the majority of patients with neuropathic pain according to the survey results had active disease according to BASDAI and ASDAS-ESH scores. We can interpret these results as contributing to the neuropathic pain component of active disease.

In this study, a positive and significant correlation was found between ASQoL, MASES, BASFI, BASDAI, ASDAS-ESH parameter scores, and PainDetect and LANSS questionnaire scores. In a study conducted in our country that included 100 AS patients, a positive correlation was found between the PainDetect questionnaire results and BASDAI, ASDAS-CRP, ASDAS-ESH, BASFI, and MASES scores²⁶. Choi et al. also examined the correlation between PainDetect scores and disease parameters, similar to our study, and found a positive correlation with BASDAI, similar to our study, and emphasized that quality of life was negatively affected²⁴. These findings show us that neuropathic pain negatively affects quality of life and functionality and that high disease activity or active disease may trigger neuropathic pain.

The research has some limitations. Firstly, the emotional states of the participants were not evaluated. Although the participants did not have known psychological diseases, the emotional states of the participants could be evaluated from a neuroscience perspective on pain. Future research will take this into account. Secondly, the medial and lateral plantar nerves, which are affected earlier in distance-dependent polyneuropathies, are not evaluated. The absence of a healthy control group is another limitation. Lastly, we could not compare the neuropathic pain scores of the participants using biological drugs and patients who did not, because the number of patients using conventional drugs was low.

In conclusion, AS patients have a significant neuropathic pain component and peripheral nerves are affected in AS. Neuropathic pain hurts the quality of life, functional status, and physical examination findings of AS patients. Disease activity is significantly higher in patients with neuropathic pain. In this case, whether high disease activity causes neuropathic pain or the presence of neuropathic pain results in high disease activity. We believe that studies with a higher number of patients, participants with inactive disease activity that can reveal the damage, and a healthy control group are needed. However, it should be emphasized that neuropathic pain is a component that should always be kept in mind in the evaluation of patients with AS.

Ethics approval

The study was approved by the Institutional Ethical Review Board of the Sivas Cumhuriyet University (approval no. 2019-09/02) and aligned with the principles outlined within the Declaration of Helsinki.

Consent to participate

All necessary explanations were given to the participants in the study and their written informed consent was obtained.

Authors' contributions

Seda Atik contributed to the conception, study design, data collection and analysis, interpretation and writing the manuscript. Ozlem Sahin contributed to the conception, study design, data collection, writing the manuscript and revision of drafts for submission. Irfan Atik contributed to the data collection, data analysis and interpretation, writing the manuscript and revision of drafts for submission. Musa Polat contributed to the conception, study design, interpretation of the data, writing of the manuscript and revision of drafts for submission. All authors read and approved the final version of the manuscript and are accountable for all aspects of this work.

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