Association of Serum Interleukin-17 and Interleukin-23 Levels with Disease Activity, Function, Mobility, Enthesitis Index in Patients with Ankylosing Spondylitis

Assoziation von Serum-Interleukin-17- und Interleukin-23-Spiegeln mit Krankheitsaktivität, Funktion, Mobilität, Enthesitis-Index bei Patienten mit ankylosierender Spondylitis

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ABSTRACT

Aim: More and more studies have demonstrated that the interleukin (IL)-23/IL-17 axis is highly associated with immune dysfunction and activated autoimmune inflammation. The purposes of this study were to determine the serum levels of IL-17 and IL-23 in ankylosing spondylitis (AS) patients compared with healthy controls and evaluate these cytokine levels based on disease-related characteristics. Material and Methods: Eighty-six consecutive AS patients and 70 sex and age-matched healthy controls were included in the study. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Ankylosing Spondylitis Disease Activity Score (ASDAS)-erythrocyte sedimentation rate (ESR), ASDAS-C reactive protein, the Bath Ankylosing Spondylitis Functional Index (BASFI), the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index, the Bath Ankylosing Spondylitis Metrology Index (BASMI), the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) and Achilles pain VAS scores were recorded. Serum IL-17 and IL-23 levels were examined by enzyme-linked immunosorbent assay. Results: The serum levels of IL-17, IL-23 and CRP as well as ESR values were significantly increased in AS patients compared with controls (1.94 vs. 0.28 pg/mL $p<0.001$; 82.9 vs. 44.3 pg/mL $p<0.001$; 0.48 vs. 0.30 mg/dL, $p=0.001$; 12 ± 13.9 vs. 8 ± 6.8 mm/h, $p=0.003$, respectively). In AS patients, serum IL-17 levels were significantly correlated with the ASDAS-ESR and ASDAS-CRP ($r=0.244$, $p=0.024$; $r=0.258$, $p=0.017$), but not with ESR, CRP, BASDAI, function, mobility, quality of life, enthesitis index or Achilles pain scores (all $p>0.05$). Serum IL-23 levels demonstrated a significant correlation with Achilles pain VAS, but not with other disease-related parameters (all $p>0.05$). Conclusions: AS patients had increased serum IL-17 and IL-23 levels compared with healthy controls, and serum IL-17 levels were associated with disease activity. Our study results support the hypothesis that the IL17/23 pathway plays an important role in the pathogenesis of AS.

ZUSAMMENFASSUNG

Ziel der Arbeit: Immer mehr Studien zeigen, dass die Interleukin(IL)-23/IL-17-Achse in hohem Maße mit einer Immundysfunktion und einer aktivierten Autoimmunentzündung assoziiert ist. Ziel dieser Studie war die Bestimmung der Serumspiegel von IL-17 und IL-23 bei Patienten mit ankylosierender Spondylitis (AS) im Vergleich zu gesunden Kontrollprobanden und die Bewertung dieser Zytokinspiegel anhand von krankheitsbezogenen Merkmalen. Material und Methoden: Sechsundachtzig konsekutive AS-Patienten und 70 gesunde Kontrollprobanden gleichen Geschlechts und Alters wurden in die Studie eingeschlossen. Dokumentiert wurden der Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), der Ankylosing Spondylitis Disease Activity Score (ASDAS)-Erythrozytensedimentationsrate (ESR), ASDAS-C-reaktives Protein (CRP), der Bath Ankylosing Spondylitis Functional Index (BASFI), der Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis-Index, der Bath Ankylosing Spondylitis Metrology Index (BASMI), der Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) sowie Achillessehnenschmerz-Scores (VAS). Die Serumspiegel von IL-17 und IL-23 wurden mithilfe eines enzymgebundenen Immunadsorptionstests untersucht. Ergebnisse: Die Serumspiegel von IL-17, IL-23 und CRP sowie die ESR-Werte waren bei AS-Patienten im Vergleich zu den Kontrollen signifikant erhöht (1,94 vs. 0,28 pg/ml, $p < 0{,}001$; 82,9 vs. 44,3 pg/ml, $p < 0{,}001$; 0,48 vs. 0,30 mg/dl, $p = 0{,}001$; 12 ± 13,9 vs. 8 ± 6,8 mm/h, $p = 0{,}003$). Bei AS-Patienten korrelierten die IL-17-Spiegel im Serum signifikant mit ASDAS-ESR und ASDAS-CRP ($r = 0{,}244$, $p = 0{,}024$; $r = 0{,}258$, $p = 0{,}017$), aber nicht mit ESR, CRP, BASDAI, Funktion, Mobilität, Lebensqualität, Enthesitis-Index oder Achillessehnenschmerz-Scores (alle $p > 0{,}05$). Die Serum-IL-23-Spiegel zeigten eine signifikante Korrelation mit der VAS Achillessehnenschmerz, aber nicht mit anderen krankheitsbezogenen Parametern (alle $p > 0{,}05$). Schlussfolgerung: AS-Patienten hatten im Vergleich zu den gesunden Kontrollpersonen erhöhte IL-17- und IL-23-Serumspiegel und die IL-17-Serumspiegel waren mit der Krankheitsaktivität assoziiert. Unsere Studienergebnisse unterstützen die Hypothese, dass der IL17/23-Signalweg eine wichtige Rolle bei der Pathogenese von AS einnimmt.

Introduction

Ankylosing spondylitis (AS) is a progressive common inflammatory disease, part of the spondylarthritis group (SpA), characterized, besides enthesitic inflammation, by new bone formation, that can be associated with both spinal and peripheral involvement [1].

Although the exact etiology and pathogenesis mechanisms are not clear, many studies have instructed that the occurrence of AS is closely related to the positive expression of human leukocyte antigen (HLA)-B27. Immune system also promotes the development and progression of AS, which can be characterized by overexpression of inflammatory cytokines and abnormal activation of immune cells in AS patients [2]. In addition to HLA-B27, two further genetic loci have been associated with AS and might be of functional relevance: endoplasmic reticulum aminopeptidase (ERAP), which encodes an aminopeptidase expressed in the endoplasmic reticulum and is involved in preparing peptides for MHC class 1 presentation to immune effector cells, and the interleukin (IL)-23 receptor, which activates T-helper (Th) cells secreting the cytokine IL-17 but also other proinflammatory cells [3, 4]. Single nucleotide polymorphisms in cytokines, their receptors, and their intracellular signaling molecules identified tumor necrosis factor alpha (TNF-α), IL-1, IL-6 and IL-23/IL-17 as cytokine pathways of major interest [5].

The pro-inflammatory cytokines IL-23 and IL-17 play an important role in activating the immune response in the host defense against pathogens and maintaining barrier functions of mucosal surfaces. Over the past several years, genetic, experimental, and clinical evidence that SpA was triggered by pathological activation of the IL-23/IL-17 axis has accumulated [6]. In the present study, we aimed to evaluate the serum levels of IL-17 and IL-23 in AS patients compared to healthy controls and to determine the association of these cytokines with disease activity, function, mobility, enthesitis index, and quality of life in patients with AS.

Material And Methods

This cross-sectional study was carried out between April 2016 and March 2017. A total of 86 AS patients (mean age 40.3 ± 12.06; F/M 30/56) who met the Modified New York diagnosis criteria were included in the study [7]. Among them, 28 patients were receiving non-steroidal anti-inflammatory drugs (NSAIDs) and 58 patients were receiving biological agent therapy. A total of 70 healthy subjects (41 ± 11.7; F/M 17/53) were included as controls. The study was approved by the local ethics committee of our institution and conducted in compliance with the principles of the Declaration of Helsinki. All participants gave written informed consent to participate the study.

Clinical evaluation

The demographic and clinical characteristics of all participants were recorded. Disease activity was measured via the self-administered 6-question Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [8] (0: no disease activity, 10: the highest disease activity), the Ankylosing Spondylitis Disease Activity Score (ASDAS)-erythrocyte sedimentation rate (ESR), and ASDAS-C reactive protein (CRP) [9]. Patients with a BASDAI ≥ 4 were defined as having active disease. Functional capacity was measured via the self-administered 10-question Bath Ankylosing Spondylitis Functional Index (BASFI) (0: lowest activity, 10: the highest activity) [10]. Spinal mobility was evaluated by Bath Ankylosing Spondylitis Metrology Index (BASMI) [11]. Score range is 0–10, with higher the BASMI score reflecting more severe the patient's limitation of movement due to their AS. The Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index was used to assess the severity of enthesitis (overall score 0–16) [12]. This index was calculated by the evaluation of following 16 enthesitis sites: the greater trochanter right/left (R/L), quadriceps tendon insertion into the patella (R/L), patellar ligament insertion into the patella and

tibial tuberosity (R/L), Achilles tendon insertion (R/L), plantar fascia insertion (R/L), medial and lateral epicondyles (R/L) and the supraspinatus insertion (R/L). Tenderness at each site was quantified on a dichotomous basis: 0 = non-tender and 1 = tender. The Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) is used to assess the impact of AS on quality of life [13]. Score range is 0–18, with higher scores reflecting greater impairment of health-related quality of life. Achilles pain intensity was evaluated using a 10-cm horizontal visual analog scale (VAS).

Laboratory analysis

The serum CRP level was measured using the Abbott auto-analyzer (Architect C1600; Abbott, USA). A normal CRP interval was defined as ≤ 0.5 mg/dL.

To determine the serum IL-17, IL-23 levels, blood samples were collected in the morning after an overnight fast from both patients and controls. After centrifugation, the serum was obtained and stored at −80 degrees until the analysis. IL-17 ve IL-23 concentrations were measured using a commercially available human IL-17 enzyme-linked immunosorbent assay kit (Abcam Inc, Cambridge, MA, USA) according to the directions provided by the manufacturer. Cytokine levels were recorded as pg/dL.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 18.0, for Windows (SPSS, Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation. Compliance of the variables with normal distribution was assessed by the Kolmogorov-Smirnov test. Inter-group analyses were performed with Student's t-test for normally distributed variables and the Mann-Whitney U test for non-parametric variables. Spearman's rank or Pearson's correlation analyses were performed to determine the correlation between the variables according to the distribution of the data. A p value of < 0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of the AS patients are demonstrated in ▶ **Table 1**. No significant difference was observed between the groups in terms of age, gender, and BMI (age: 40.3 ± 12.05 vs 41.0 ± 11.77 years, p = 0.758; female/male: 30/56 vs 17/53, p = 0.208; BMI: 27.7 ± 3.6 vs 26.8 ± 2.9, p = 0.184, respectively). The mean BASDAI, ASDAS-ESR, and ASDAS-CRP were 2.68 ± 2.47, 2.14 ± 1.06, and 2.19 ± 1.04, respectively. HLA-B27 positivity was observed in 77.9 % of the patients with AS. In addition, 28 patients were receiving NSAIDs and 58 patients were receiving biological agents. The biological agents used included adalimumab in 16 patients, etanercept in 22 patients, infliximab in 13 patients, and golimumab in 7 patients.

The median serum levels of IL-17, IL-23, and CRP values significantly increased in AS patients compared to controls (1.94 vs 0.28 pg/dL p < 0.001; 82.96 vs 44.3 pg/dL p < 0.001; 0.48 vs 0.30 mg/dL, p = 0.001, respectively) (▶ **Table 2**). The mean ESR values also increased in AS patients compared to controls (12 ± 13.9 vs 8 ± 6.8 mm/h, p = 0.003).

When the patients were classified into two subgroups according to the types of medication they received (NSAIDs: 28 patients, biological agents: 58 patients), no significant difference was observed between AS patients with NSAIDs and biologic agents in terms of the serum IL-17, IL-23, ESR, and CRP values (data not showed, all p > 0.05). In addition, the median BASDAI and ASQoL were significantly higher in the NSAIDs group than those in the biological agents group (3.35 vs 1.42 p = 0.011; 7 vs 2 p = 0.035, respectively).

Of the AS group, 22 patients were in the active status based on the BASDAI score, while 64 patients were in the inactive status. A comparison of the active AS group with the inactive AS group revealed out that active AS patients had significantly higher ESR, CRP,

▶ **Table 1** Demographic and clinical characteristics of patients with ankylosing spondylitis

AS patients	**(n = 86)**
Age (years), mean ± SD	40.3 ± 12.06
Sex (Female/male) n (%)	56/30 (34.9/65.1)
BMI (kg/m^2), mean ± SD	27.7
Disease duration (years), median	4 (0.8–33)
HLA-B27 positivity n (%)	67 (77.9)
History of uveitis n (%)	17 (19.8)
Family history n (%)	28 (32.6)
History of peripheral arthritis n (%)	24 (27.9)
BASDAI (mean ± SD)	2.68 ± 2.47
active disease n (%)	22 (25.6)
inactive disease n (%)	64 (74.4)
BASFI (median) (min-max)	1.05(0–10)
BASMI(median) (min-max)	0.00 (0–9)
ESH mm/h (mean ± SD)	16.15 ± 13.92
CRP mg/dL(median) (min-max)	0.48 (0.1–8.9)
ASDAS-CRP (mean ± SD)	2.19 ± 1.04
ASDAS-ESH(mean ± SD)	2.14 ± 1.06
ASQoL, median (range)	4.0 (0–17)
SPARCC, median (min-max)	0 (0–16)
Achilles pain-VAS median (min-max)	0 (0–5)
Medication n (%)	
NSAIDs (%)	28 (32.6)
Biological agents, n (%)	58 (67.4)
Infliximab	13 (22.4)
Adalimumab	16 (27.6)
Etanercept	22 (37.9)
Golimumab	7 (12.1)

AS ankylosing spondylitis, *SD* Standard deviation, *BMI* body mass index, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index SPARCC Spondyloarthritis Research Consortium of Canada, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *ASQoL* Ankylosing Spondylitis Quality of Life Questionnaire, *NSAIDs* non-steroidal anti-inflammatory drugs,

▶ **Table 2** The comparison of the cytokine levels beetween AS patients and healthy controls

	AS (n = 86)	Control (n = 70)	p
Age, (years), mean ± SD	40 ± 12.1	41 ± 11.8	0.758
IL-17 (pg/dL), median	1.94	0.28	< 0.001
IL-23 (pg/dL), median	82.96	44.33	< 0.001
ESH (mm/h) mean ± SD	12 ± 13.9	8 ± 6.8	0.003
CRP (mg/dL) median	0.48	0.3	0.001

AS ankylosing spondylitis, *IL* interleukin, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

▶ **Table 3** The comparison of AS patients with active disease and inactive disease based on BASDAI scores

	AS with active disease (n = 22)	AS with inactive disease (n = 64)	p
Age (years), mean ± SD	44.9 ± 11.7	38.8 ± 11.8	
IL-17 (pg/dL), median	2.24	1.78	0.161
IL-23 (pg/dL), median	64.88	89.90	0.035
CRP (mg/dL), median	0.79	0.35	0.025
ESH (mm/h), median	22	9	0.001
BASFI, median	4.75	0.7	< 0.001
BASMI, median	1	0	0.080
ASDAS-CRP, mean ± SD	3.5 ± 0.8	1.7 ± 0.7	< 0.001
ASDAS-ESH, mean ± SD	3.6 ± 0.8	1.6 ± 0.6	< 0.001
ASQoL, median	12.5	2.0	< 0.001
SPARCC, median	4	0	0.001
Achilles pain-VAS, (range)	0 (0–5)	0 (0–1)	0.009

AS ankylosing spondylitis, *IL* interleukin, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *ASQoL* Ankylosing Spondylitis Quality of Life Questionnaire, *SPARCC* Spondyloarthritis Research Consortium of Canada

BASFI, ASDAS-ESR, ASDAS-CRP, ASQoL, SPARCC enthesitis index, and Achilles pain-VAS scores compared to inactive AS patients (for all $p < 0.05$) (▶ **Table 3**). Although there was no significant difference in serum IL-17 levels between the groups, serum IL-23 levels significantly elevated in inactive AS patients compared to active AS patients (89.9 vs 64.8 $p = 0.035$).

The correlations of the serum cytokine levels with disease related variables are demonstrated in ▶ **Table 4**. Serum IL-17 levels were significantly correlated with the ASDAS-ESR and ASDAS-CRP ($r = 0.244$, $p = 0.024$; $r = 0.258$, $p = 0.017$). However, no correlation was detected between the serum IL17 levels and ESR, CRP, BASDAI, BASFI, BASMI, ASQoL, or SPARCC enthesitis index (all $p > 0.05$). Serum IL-23 levels demonstrated significant correlation with Achilles pain-VAS ($r = 0.262$, $p = 0.015$), but not with other disease related parameters (all $p > 0.05$).

Discussion

This study results demonstrated that AS patients had increased serum IL-17 and IL-23 levels compared to controls and serum IL-17 levels associated with disease activity but not with other disease related parameters.

Increasing studies have demonstrated that IL-23/IL-17 axis was highly associated with immune dysfunction and activated autoimmune inflammation [2]. Further studies demonstrated that IL-23/IL-17 axis contributes to the development of several inflammatory diseases, such as rheumatoid arthritis, psoriasis, psoriatic arthritis, AS, inflammatory bowel disease, sjogren syndrome, multiple sclerosis [14]. IL-23 is a heterodimeric cytokine that consists of a p40 subunit, which it shares with IL-12, and a p19 subunit. The IL-17 family consists of IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F, of which IL-17A, commonly referred to as IL-17, is the best characterized member [15]. The main source of IL-17 A and IL-17 F is type 17 Th (Th17) cells, which also produce cytokines such as IL-22 and IL-21 [16]. Differentiation of Th17 cells is regulated by a combination of cytokines, such as IL-1β, IL-6, transforming growth factor-β and especially IL-23. Th17 cells release several cytokines, represented by IL-17–A, IL-17 F, IL-22, IFN-γ, or granulocyte-macrophage colony-stimulating factor [1]. The IL-17 members may combine with the IL17Rs [16], and then activate various inflammatory pathways, including the nuclear factor κB pathway, the mitogen-activated protein kinases pathway, and the CCAAT/enhancer-binding proteins pathway [17]. The activation of these signal transduction pathways leads to the overexpression of various proinflammatory cytokines, such as IL-6, IL-8, TNF-α, and IL-1β [18].

In the present study, we found significantly elevated serum IL-17 and IL-23 levels in AS patients compared to healthy controls. These findings are in accordance with the results of previous studies [19–23]. Milanez et al. also showed that the active AS group presented significantly higher IL-23 levels compared with healthy controls although no difference was observed in plasma IL-17 levels between patients with AS and healthy controls [24]. In contrast to our results, Sveas et al. [25] reported no significant difference in serum IL-17 and IL-23 levels while Deveci et al. [26] reported the decreased levels of these cytokines in AS patients compared to healthy controls.

The association of these cytokine levels with various disease related factors such as disease activity, function, mobility, enthesitis index, treatment agents, quality of life, or Achilles pain were also evaluated in the present study. Serum IL-17 levels were significantly correlated with ASDAS-ESR and ASDAS-CRP, but not with BASDAI, ESR, CRP, disease duration, function, spinal mobility, quality of life, enthesitis index, or Achilles pain. It has been reported that ASDAS correlated more with inflammatory biomarkers than BASDAI [27]. In addition, there was a significant correlation between serum IL-23 levels and Achilles pain in the present study. However,

▶ **Table 4** The association of serum IL-17 and IL-3 levels with disease related variables in AS patients

	IL-17 r	p	IL-23 r	p
Age (years)	−0.400	0.714	−0.480	0.659
Disease duration, years	−0.082	0.455	−0.066	0.548
ESR (mm/h)	0.175	0.107	−0.122	0.261
CRP(mg/dL)	0.182	0.096	−0.104	0.345
BASDAI	0.190	0.079	−0.199	0.066
ASDAS-ESR	0.244	0.024	−0.107	0.328
ASDAS-CRP	0.258	0.017	−0.122	0.265
BASFI	0.185	0.087	−0.003	0.980
BASMI	−0.023	0.835	0.165	0.128
ASQoL	0.079	0.471	−0.059	0.589
SPARCC	−0.099	0.367	0.033	0.761
Achilles pain-VAS	−0.073	0.501	0.262	0.015

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index *ASDAS* Ankylosing Spondylitis Disease Activity Score, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *ASQoL* Ankylosing Spondylitis Quality of Life Questionnaire, *SPARCC* Spondyloarthritis Research Consortium of Canada

no significant correlation was found IL-23 and other disease related parameters. Melis et al. also reported that systemic levels of IL-23 are strongly associated with disease activity in RA but not SpA [28]. In the study by Chen et al., serum IL-17 and IL-23 levels both correlated with BASDAI, but did not correlated with functional ability and spinal mobility in patients with AS [19]. In an another study by Taylan et al., IL-17 did not correlated with BASFI, BASDAI, BASMI, disease duration, or CRP values in patients with AS [23]. In addition, IL-23 levels showed significant correlation with BASMI but not with other parameters in that study. No significant association of disease activity with IL-23 or IL-17 levels also demonstrated in previous other studies [21, 25, 27]. We also demonstrated that although serum levels of IL-17 did not differ between active and inactive AS patients, IL-23 levels significantly increased in inactive AS patients, contrary to expectation. No significant difference in serum IL-17 and IL-23 levels between active and inactive AS patients has been reported in other two studies [21, 23]. It has been suggested that IL-23 exerts a role only in initiating pathological process, both for AS or axial SpA, and not in perpetuating the damage in established disease [1]. In contrast, Chen et al. demonstrated that patients with active AS had significantly higher serum IL-17 and IL-23 levels compared with inactive AS patients [19]. The controversial results among these studies mentioned above might be attributed to the different method of analysis and study samples in terms of age, gender, disease duration, or treatment agents.

In our AS cohort, we also found no significant differences in serum IL-17 and 23 levels between patiens treated with NSAIDs and biological agent, in accordance with findings from the study by Taylan et al. [23]. Milanes et al. also demonstrated that after 24-months of TNF blockade, IL-23 levels remained elevated with higher levels in active AS group compared with the healthy in spite of significant improvements in all clinical/inflammatory parameters in their study [24]. Most of the reported studies on this subject in the literature have not presented any data of patients' treatment [19–21] or did not consist of AS patients under biological agent [22, 26].

Major limitation of the present study is the absence of these cytokine analyses in inflammatory tissue or synovial fluid which could provide more accurate clarification of the cytokine levels with disease related parameters. Also, the sample size was relatively small and the patients were on different treatment modalities which could affected the serum cytokine levels and the association of these cytokines with other variables. Because of the cross-sectional study design, we could not evaluated serum cytokine levels at baseline and post-treatment with biological agents.

In conclusion, the present study revealed the increased serum IL-17 and IL-23 levels in AS patients compared to healthy controls and the significant association of IL-17 levels with disease activity. Our study results support that IL17/23 pathway plays an important role in the pathogenesis of AS.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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