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Brucellosis; Difficulty of Diagnosis in Endemic Areas

Bruselloz; Endemik Bölgelerde Tanı Zorluğu

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Abstract

Introduction: Brucellosis is a zoonotic disease distributed worldwide and very important public health problem especially in the developing countries. In this study, we aimed to evaluate the clinical/laboratory findings of brucellosis patients and contribute of coombs testing to diagnosis at Iğdır State Hospital's Infection Diseases and Clinical Microbiology department.

Material and Method: One hundred and forty-five brucellosis patients followed up in our clinic between September 2012 and February 2013 were evaluated retrospectively. Demographic characteristics, laboratory findings, diagnostic methods of the patients were presented.

Results: The mean age of the patients were 39±15 (18-80) and 59% (n=86) of the patients were female, 41% (n=59) were male. Most frequent risk factors were animal breeding (n=115, 79%) and using underdone milk and milk products (n=98, 69%). Most reported complaints were weakness (92%), arthralgia (89%), sweating (74%), lack of appetite (70%) and fever (68%). Fifty-seven of the brucellosis patients could not diagnosed with standard tube agglutination. Therefore, Coombs test was used for these undiagnosed patients (39%, n=57). Eighty patients were evaluated as acute (55%), 53 as subacute (37%) and 12 as chronic (8%) brucellosis.

Conclusion: Brucellosis can affect all organ systems and cause different clinical manifestations. Therefore, difficulties are encountered in the diagnosis of the disease. Brucellosis should be kept in mind in the differential diagnosis especially in the endemic regions. When the clinical suspicion exists detailed laboratory evaluation must be performed.

Keywords: Brucellosis, diagnosis, coombs test.

Öz

Giriş: Bruselloz tüm dünyada yaygın olarak görülen zoonotik bir hastalıktır ve özellikle gelişmekte olan ülkelerde çok önemli bir halk sağlığı sorunudur. Bu çalışmada, Iğdır Devlet Hastanesi Enfeksiyon hastalıkları ve klinik mikrobiyoloji bölümünde takipli bruselloz hastalarının klinik/laboratuvar bulgularının ve coombs testinin tanıya katkısının değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Eylül 2012-Şubat 2013 tarihleri arasında kliniğimizde izlenen 145 bruselloz hastası geriye dönük olarak değerlendirildi. Hastaların demografik özellikleri, laboratuvar bulguları, tanı yöntemleri sunuldu.

Bulgular: Hastaların yaş ortalaması 39±15 (18-80) olup, hastaların %59'u (n=86) kadın, %41'i (n=59) erkekti. En sık görülen risk faktörleri hayvancılık (n=115, %79) ve az pişmiş süt ve süt ürünleri kullanımıydı(n=98, %69). Bildirilen şikayetlerin çoğu halsizlik (%92), artralji (%89), terleme (%74), iştahsızlık (%70) ve ateş (%68) idi. Hastaların %60,6'sında (n=88) standart tüp aglutinasyonu pozitifti (≥ 1/160 titrasyonda), 57'sine standart tüp aglütinasyonu tanısı ile konulamadığından bu hastalarda Coombs testi kullanıldı (%39, n=57). Seksen hasta akut (%55), 53 hasta subakut (%37) ve 12 hasta kronik (%8) bruselloz olarak değerlendirildi.

Sonuç: Bruselloz tüm organ sistemlerini etkileyebilir ve farklı klinik bulgulara neden olabilir. Bu nedenle hastalığın tanısında güçlüklerle karşılaşılmaktadır. Özellikle endemik bölgelerde ayırıcı tanıda bruselloz akılda tutulmalıdır. Klinik şüphe mevcut olduğunda ayrıntılı laboratuvar değerlendirmesi yapılmalıdır.

Anahtar Kelimeler: Bruselloz, tanı, coombs testi

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INTRODUCTION

Brucellosis is a zoonosis that seen commonly all over the world, and continues to be an important health problem for developing countries.[1] It is endemic in Turkey, particularly concentrated in Central Anatolia, Eastern and Southern Anatolian cities.[2]

Brucellosis can involve all organs and systems, cause different clinical pictures, so diagnosis may be difficult.[3]

The gold standard method in the diagnosis of brucellosis is culture;however, its sensitivity decreases depending on several factors (e.g.disease duration and history of antibiotic use). For this reason, serological methods such as Rose-Bengal Test -as a screening test-, Standard Tube Agglutination (STA), and Coombs'Antiglobulin Test are often used for diagnosis.[4]

In this study, we aimed to evaluate brucellosis cases that followed-up at Iğdır State Hospital, which is a small city in northeastern Turkey. and importance of Coombs test for diagnosis of brucella cases that cannot be detected by screening test in hospitals where blood culture is not possible.

MATERIAL AND METHODS

One hundred and forty-five adult patients that followed-up at infectious diseases department with a diagnosis of brucellosis between September 2012 and February 2013 were retrospectively evaluated. The age, sex, risk factors, complaints, duration of complaints, physical examination and laboratory findings were recorded.

The inclusion criteria were as follows:[5]

- Serum agglutination titer over 1/160 with clinical sign and symptoms, or
- Coombs test over 1/160 with clinical sign and symptoms, or
- Brucella spp positivity in blood culture.

Patients under the age of 18, and patients treated for brucellosis in the past year were excluded.

For the serologic diagnosis, slide antigen that was produced by Turkish Public Health Institution (TPHI) was used for Rose Bengal test, and B. abortus antigen (that was also produced by TPHI) was used for STA. The STA was prolonged until a negative tube was seen in each sample. The agglutination test with the Coombs serum was used to prevent blocking antibodies and eliminating false negativity. The Coombs Test was used in every patient who could not be diagnosed with STA but was clinically considered to have brucellosis. Blood cultures were incubated for seven days in BACTEC9120 (Becton-Dickinson) system and conventional methods were used to identify microorganisms.

Consuming rare-cooked milk and dairy products, working in livestock, being a butcher, veterinarian or laboratory worker were accepted as the risk factors for the disease. Patients were classified as acute (less than 8 weeks), subacute (8-52 weeks), and chronic (more than 52 weeks) according to duration of clinical symptoms.

Statistical Analysis

Statistical analysis was performed using the SPSS v15.0 package program. In descriptive statistics, the continuous variables were expressed as mean and standard deviation and the categorical variables were expressed as frequencies and percentages. The Kolmogorov-Smirnov test was used to assess the normality of the data. ESR values were distributed normally, and this variable was compared with one-way ANOVA test between disease duration groups (acute, subacute, chronic). Since CRP and ferritin values were not normally distributed, these variables were compared with Kruskal-Wallis test between groups. A p value of <0.05 was considered statistically significant.

The study was carried out with the permission of Diskapi Yildirim Beyazit Training and Research Hospital Ethics Committee (Date: 27.06.2016, Decision No: 31/04). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

RESULTS

When the demographic characteristics of 145 cases of the study were evaluated, mean age was 39±15 (18-80) years, 59% (n=86) were females, and 41% (n=59) were males. Risk factors were livestock (n=115, 79%), consuming raw milk and dairy products (n=98, 69%) and being butcher (n=5, 3%).

Eighty (55%) patients had acute, 53 (37%) had subacute, and 12 (8%) had chronic brucellosis, 26% (n=38) had a history of brucellosis longer than one year ago, and 36% (n=53) had family history. When the complaints at first admission were evaluated, the most frequent symptoms were found to be weakness, arthralgia and sweating (**Table 1**). Physical examinations revealed fever over 38.3°C in 42 (29%) patients, hepatomegaly in 20 (14%), splenomegaly in 10 (7%), hepatosplenomegaly in six (4%), peripheral arthritis in six (4%), and erythema nodosum in two (1.4%) patients. Correlation between organomegaly and disease duration was summarized in **Figure 1**. Splenomegaly was more frequent in acute brucellosis cases. Hepatomegaly was detected in all periods of the disease.

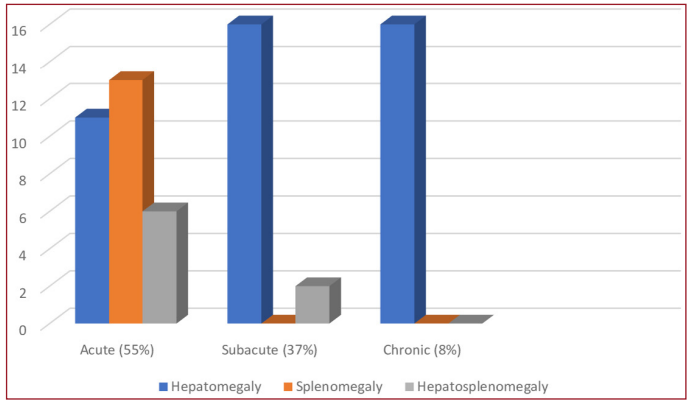

Figure 1: Disease durations of patients with organomegaly

Table 1: Patients' symptoms	
Symptoms	**n (%)**
Weakness	134 (92)
Arthralgia	129 (89)
Sweating	107 (74)
Loss of appetite	101 (70)
Fever	99 (68)
Headache	93 (64)
Lumbalgia	92 (63)
Myalgia	62 (43)
Stomachache	53 (37)
Weight loss	32 (22)
Joint swelling	25 (17)
Scrotal pain	6 (10)

The serologic tests revealed that Rose Bengal test was negative in 16 patients, and STA test was lower than 1/160 in 57 (39%) patients.They applied to the polyclinic after an average of one month after the onset of the compliant. STA was not repeated, as there was admission more than two weeks after the onset of symptoms. Both Rose Bengal and STA tests were found negative in 14 (9.7%) cases. STA test was 1/160 in 32 (22%), 1/320 in 44 (30%), 1/640 in seven (5%), 1/1280 in four (3%), and 1/5120 in one (0.7%) cases. Fifty-seven cases that could not be diagnosed with STA test were diagnosed by the Coombs test (**Table 2**). Thirty-six percent (n=29) of acute cases, 40% (n=21) of subacute cases, and 58% (n=7) of chronic cases were diagnosed with the Coombs test. In four acute cases with positive blood cultures, STA test was below 1/160 and the diagnosis was confirmed with the Coombs test. Blood cultures were obtained from only 28 cases due to the unavailability of the hospital resources, and 17 (60.7%) had positive results (**Table 2**). Of importance, we have noticed that 65% of positive blood cultures were obtained from patients without fever. Of the cases with positive blood culture, 14 (82%) were acute, and 3 (18%) were subacute brucellosis cases. Laboratory findings were summarized in **Table 3**. The assessment of ferritin levels revealed that 24 of the 112 cases (21%) had elevated ferritin levels.The elevations detected in the acute phase reactants decreased to the normal limits following the treatment - in all patients. The effect of disease duration on factors such as age, blood culture, and serological test positivity, and the elevation in acute phase reactants are discussed in **Table 4**. Comparisons of disease durations of cases with increased ESR, CRP, and ferritin were shown in **Figure 2**. The increases in these values were found to be significantly higher in acute brucellosis when compared to subacute and chronic brucellosis ($p<0.05$).

Table 2: The results of diagnostic tests performed			
Test performed	**Number of tests performed**	**Negative result (%)**	**Positive result (%)**
Rose Bengal	145	16 (11%)	129 (89%)
STA*	145	57** (39.3%)	88*** (60.7%)
Coombs Agglutination	57	-	57***
Blood culture	28	11 (39.3%)	17 (60.7%)

*STA: Standard Tube Agglutination, **< 1/160 recorded as negative, ***1/160 and above recorded as positive

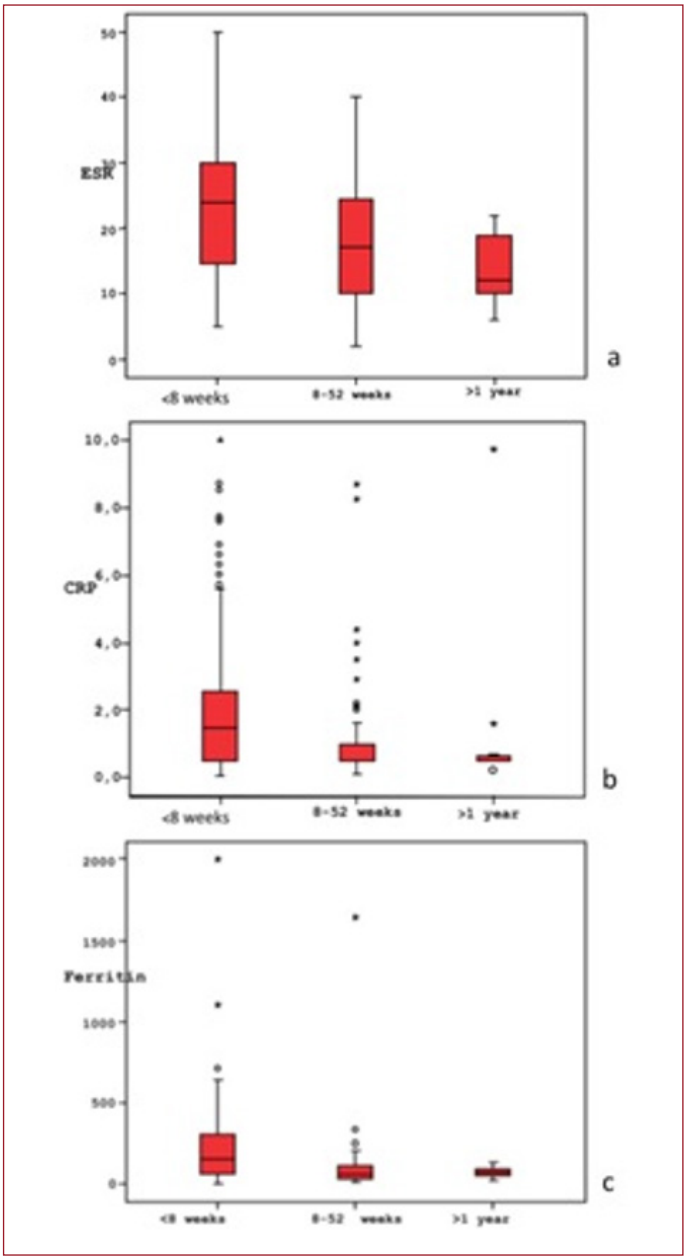

Figure 2. Comparison of disease durations of patients with (a) ESR, (b) CRP, and (c) fernitin

Table 3: Patients' laboratory findings	
Laboratory finding	**n (%)**
Anemia (women: <12 mg/dl; men: <14 mg/dl)	27 (19)
Leucopenia (<4500/mm³)	18 (12)
Lymphomonocytosis	67 (46)
Leukocytosis (>10500/mm³)	9 (6)
Thrombocytopenia (<150000/mm³)	16 (11)
ESR (>20 mm/h)	75 (52)
CRP (>1 mg/dl)	65 (45)
Ferritin (women >150ng/ml; men > 400 ng/ml)	24 (17)
ALT (>40 IU/L)	51 (35)
AST (>40 IU/L)	34 (23)

ESR: Erythrocyte sedimentation rate, CRP: C reactive protein, ALT: Alanine transaminase, AST: Aspartate transaminase

Table 4: Comparison of age and laboratory findings of patients with Brucellosis according to disease duration. Data presented as mean±standard deviation, median (min-max) or percent

	Acute	Subacute	Chronic	p
Age (n=145)	39.22±14.89	39.38±15.74	43.42±12.27	0.659*
Positivity of blood culture % (n=17, 100%)	14, 82%	3, 18%	-	0.104**
ESR (mm/h)	23.20±10.38	13.38±10.01	20.68±10.34	<0.05*
CRP (mg/dl)	2.24±2.35	1.23±1.75	1.36±2.65	<0,05**
Leukocyte (/mm³)	6945.8±2250.1	7062.2±1903.5	7823.3±2602.3	0,425*
Hb (mg/dl)	13.81±1.78	14.16±1.01	14.16±1.01	0.753*
Rose-bengal, % (n=145)	91.3	84.9	91.7	0.498**
STA	1/160 (0-1/5120)	1/160 (0-1/1280)	1/40 (0-1/1280)	0.657**
Coombs testi	1/320 (1/160-1/1280)	1/320 (1/160-1/2560)	1/320 (1/160-1/320)	0,998**
Ferritin	230.48±297.81	127.93±272.07	70.82±31.07	<0.05**

ESR: Erythrocyte sedimentation rate, CRP: C reactive protein, Hb: hemoglobin, STA: Standart tube agglutination. Acute: Disease duration shorter than 8 weeks, Subacute: Disease duration 8 weeks 1 years, Chronic: Disease duration more than 1 year, *:ANOVA test, **:Kruskall-Wallis test

DISCUSSION

Brucellosis is a zoonotic disease seen worldwide. Each year, it is estimated that more than 500000 new cases are diagnosed and its prevalence is more than 1/100000 in endemic countries. It is hyper-endemic in Mediterranean countries, Arabian Peninsula, India, Mexico, and Central and South America. It is also endemic in our country, but its prevalence is unknown due to lack of reporting.[6] Çetin et al. evaluated 70000 individuals for brucellosis seropositivity, and found that 1.8% of the entire population was seropositive, and this was 6% in high-risk groups.[7] In a seroprevalence study conducted in blood donors, brucella was found at a rate of 2.7%.[8]

Brucellosis is recognized at every age and sex in Turkey, but it is more frequent especially between 15-35 years of age and in males. It is a prevalent infectious disease in animals, so it is frequently seen in people working with livestock, and consuming raw milk and dairy products.[9] In this study, which evaluated 145 cases that followed-up in our department, mean age was 39, 59% of the patients were females, and 79% were working with livestock. Sixty-eight percent of patients had a history of consuming undercooked milk and dairy products. These findings were in accordance with previous reports from Turkey and suggested that brucellosis is a highly prevalent disease in northeastern Turkey mainly due to consumption of raw milk products and not following personal protective measures when dealing with animals.[10]

Most frequent complaints of brucellosis are weakness, arthralgia, fever, sweating, and loss of appetite.[6,11-13] These complaints were found in our cases with similar frequencies. Fever was the major complaint of admission in 68% of the cases, but it was found as a physical examination finding in only 28% of cases. Similarly, Buzgan et al. found that 72.2% of cases had a complaint of fever, but only 28.8% of them had fever in physical examination.[6] This may be explained by the undulant nature of fever in brucellosis.

Every system and organ can be involved in brucellosis. In our study, hepatomegaly was present in 14%, splenomegaly was present in 7%, and hepatosplenomegaly was present in 4% of the patients. These rates were lower than previous reports.[6,12,13] When the association between organomegaly and disease duration was evaluated, splenomegaly was found to be more frequent in acute periods. Hepatomegaly was detected in all periods. Similar results were also reported in Buzgan et al. study.[6] Because hepatosplenomegaly is a result of replication of Brucella in the reticuloendothelial system, it was thought to be of splenomegaly is more frequent in acute and subacute periods.

Hematological abnormalities are frequent in brucellosis, but mostly they are not diagnostic.[2,14] Anemia, leukopenia, and lymphomonocytosis are frequent, and thrombocytopenia, pancytopenia, and disseminated intravascular coagulation are rarely seen.[11] In our study anemia was present in 19%, leukopenia in 12%, lymphomonocytosis in 46%, leukocytosis in 6%, and thrombocytopenia in 11% of the patients. These findings are compatible with other reports.[2,14]

ESR, CRP, and ferritin are known as acute phase reactants and they are used as inflammation indicators, not used for diagnosis.[15] Elevations of acute phase reactants in brucellosis were reported previously. ESR and CRP values were reported to be higher in acute and subacute cases.[3,5] Similarly, ESR and CRP elevations were more frequently found in acute and subacute cases in our study. Elevation of serum ferritin in brucellosis cases may be due to nonspecific tissue damage, and abnormalities in iron metabolism and/or hematopoiesis. Ferritin levels as high as 250 ng/L in patients with brucellosis was reported previously.[17] Serum ferritin level elevations were present in 17% (n=20) of our patients, and 88% (n=17) of these patients were in the acute period. Extremely high levels of serum ferritin as high as 2000 ng/L were detected in our patients. The correlation of disease duration and ferritin elevation has not been reported previously (**Figure 2**). These elevations may be related with the inflammatory over-response against bacterial load. The high levels were normalized after successful treatment in all cases.

Definitive diagnosis of brucellosis is based on the isolation of bacteria from clinical samples.[10] The positivity rates in blood cultures were reported between 11.4%-68.8% in previous studies.[6,11,12,18] In our study, blood cultures were taken from 28 patients, and 60.7% (n=17) of them had positive results. It was possible to obtain blood cultures from a small number of

patients because of the lack of materials in our hospital, but high positivity rates were found. It was remarkable that blood cultures were taken in the fever-free period of the patients who were positive.This shows us the importance of obtaining blood cultures when clinical findings are present, even in the absence of fever.

Of the serologic tests, Rose Bengal as screening test and STA are frequently used in the diagnosis. The sensitivity of commercially available Rose Bengal tests is between 96% and 100%. With STA, infection can be determined serologically in more than 97% of cases after three weeks of a disease period.[19] IgA and IgG antibodies, which are called as blocking antibodies, may cause false negative results.Also, false negativity can be detected in the early stages of the disease and in the Prezon Phenomenon in which agglutination may be masked at low dilution of the serum, especially when the serum has high titers of antibodies. It is frequently seen at 1/20 dilution and is rare at 1/80 and above dilutions. False positive results occur because of cross-reactivity with antibodies against Francisella tularensis, Escherichia coli O116 and O157, Salmonella urbana, Yersinia enterocolitica O: 9, Vibrio cholerae, Xanthomonas maltophilia and Afipia chevelandensis. False positive and negative results can be avoided by making dilutions of 1/320 or higher.[20] For these reasons, the STA dilutions were prolonged until there was a negative tube in the present study. The Coombs Test is used to prevent blocking anchors.[5] The cases diagnosed by Coombs Test were reported as 1%-6% in different studies.[7,21] In the study of Uysal et al., the diagnostic value of STA was reported to be low, especially in chronic patients, and it was recommended to repeat the tests with Brucellacapt and/or ELISA.[22] Coombs Agglutination Test was used in all our patients who were found to be negative for STA. The sensitivity of Rose Bengal test was found to be 89%, and STA was found positive in only 60,7% of brucellosis cases. All patients with negative STA results (n=57) were found to be positive with the Coombs test. In accordance with the literature, the contribution of the Coombs test to diagnosis was found to be more in chronic cases rather than acute and subacute cases. Diagnosis was based on Coombs test in 36% of acute cases, 40% of subacute cases, and 58% of chronic cases. Interestingly, in four acute cases with positive blood cultures, STA test was below 1/160 and the diagnosis was confirmed with the Coombs test.

The rate of cases diagnosed with the Coombs test was higher than literature, and this was thought to be related with that study was conducted in an endemic region and the Coombs test was performed more frequently by a careful evaluation of risk factors and clinical findings of patients.

Previous studies reported that diagnostic sensitivity of ELISA IgG and IgM was higher than STA.[3,18] But, Memish et al. reported that STA was more valuable in the diagnosis of brucellosis in cases with bacteremia, and should be evaluated together with ELISA IgM.[21] In our study, ELISA IgM and IgG could not be analyzed due to the limited resources.

The limitations of our study were that blood culture have not been studied for all patients (because of lack of equipment in our hospital) and ELISA IgG and IgM have not been studied for anyone (because there were no ELISA kits for brucellosis).

CONCLUSION

In conclusion, brucellosis is still an endemic disease in our country, and detailed physical examination and further analyses should be performed in the presence of a clinical suspicion since the sensitivity of screening tests are low in the acute period. ESR, CRP, elevated ferritin, and hepatosplenomegaly were found to be more frequent in acute and subacute periods of the disease. Especially in endemic regions, it should be kept in mind that contribution of screening tests and STA to the diagnosis is limited. In the presence of a clinical suspicion, Coombs test should be performed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Diskapi Yildirim Beyazit Training and Research Hospital Ethics Committee (Date: 27.06.2016, Decision No: 31/04).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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