Received: 24 Apr 2023 | **Accepted:** 29 Aug 2023 **Genel Tıp Derg. Volume** 33/**Issue** 6 (December), 699-702
DOI: 10.54005/geneltip.1287053

ORIGINAL ARTICLE

Dairy Products and Pediatric Brucellosis in Anatolia

Anadoluda Süt Ürünleri ve Pediatrik Bruselloz

[1]Kamuran Suman, [2]Ebru Gök, [3]Murat Suman, [3]Musa Büyük

[1]Afyonkarahisar State Hospital
[2]Erciyes Üniv.
[3]Cay State Hospital

Correspondence

Murat Suman, Cay State Hospital

E-Mail: muratsuman@hotmail.com

How to cite ?

Suman K, Gök E, Suman M, Büyük M. Dairy Products and Pediatric Brucellosis in Anatolia. Genel Tıp Derg. 2023;33(6):699-702.

ABSTRACT

Introduction: The aim of this study is to assess the follow-up and treatment outcomes of pediatric brucellosis cases at our participating centers during a specific period when they were diagnosed with the disease.
Methods: This research, supported by participating centers in the Central Anatolia region, was conducted over a span of approximately 2 years. We retrospectively reviewed data from patients diagnosed with brucellosis between 2018 and 2021. Patients with incomplete information in the system were excluded from the study.
Results: Based on the data collected from the participating centers, our study included a total of 68 patients who met the criteria after excluding those with incomplete information. These patients were aged between 5 and 17, with an average age of 8.7±3.1 years. Our analysis of the patients' demographics showed that they predominantly resided in rural areas where unpasteurized milk and dairy products are commonly consumed. While a few patients from higher socioeconomic backgrounds purchased organic products from local markets, the vast majority (90%) had a history of consuming unpasteurized milk and its by-products. Additionally, a significant proportion (50%) of patients from rural areas had a family history of brucellosis. The most frequently reported symptom among patients was joint pain, which was present in 83% of cases. Elevated liver enzymes were the most common laboratory finding, affecting 32% of patients, while thrombocytopenia was the least common. The preferred treatment regimen for patients was doxycycline and rifampicin. Although aminoglycoside treatment was initially favored for inpatients (80%), it was not commonly prescribed for outpatients. The data analysis revealed that only two patients experienced a relapse of the disease. While the overall treatment outcomes were successful, there was no statistically significant association between treatment preferences and disease recurrence.
Conclusion: Each year, numerous children in our country are admitted to pediatric clinics with complaints of joint pain, and this leads to extensive investigations. It is crucial to consider that with a suspicious patient history and demography, brucellosis may be the underlying cause of such symptoms, along with elevated liver enzymes and cytopenia.

Keywords: Brucellosis, Dairy products, Liver enzymes

ÖZ

Giriş: Bu çalışmanın amacı, dönem içinde katılımcı merkezlerimize başvuran ve bruselloz tanısı alan pediatrik bruselloz olgularının takip ve tedavi sonuçlarını değerlendirmektir.
Yöntem: İç Anadolu bölgesindeki katılımcı merkezlerin desteğiyle yürütülen çalışma yaklaşık 2 yılda tamamlandı. 2018-2021 yılları arasında bruselloz tanısı konmuş hastaların sonuçları retrospektif olarak tarandı. Bu tarama sırasında sistemde eksik sonuçları olan hastalar çalışmaya dahil edilmedi.
Bulgular: Katılımcı merkezlerden aldığımız bilgilere göre, kriterlerimize uyan 68 hasta çalışmamıza dahil edildi; bilgileri eksik olan hastalar çıkarıldı. Bu hastaların yaşları 5 ile 17 arasında değişmekteydi ve ortalama yaşları 8.7±3.1 olarak belirlendi. Demografik analiz, hastaların çoğunlukla kırsal kesimde yaşadığını ve pastörize olmayan süt ürünleri tüketen akrabaları olduğunu ortaya çıkardı. Elbette, bu tanıma uymayan bazı hastalarımız da vardı; yerel pazarlardan organik ürünler alan ve sosyoekonomik düzeyi daha yüksek olan hastalar. Ancak, genel olarak hastaların %90'ının pastörize edilmemiş süt ve süt ürünleri tüketimi hikayesi vardı. Aile öyküsü incelemesinde özellikle kırsal kesimde aile içi pozitiflik oranının %50 olduğu belirlendi. Hastaların semptomlarına bakıldığında en sık görülen şikayet eklem ağrısıydı (%83). Laboratuvar değerlerine göre ise en sık karşılaşılan bulgu karaciğer enzimlerinde yükselme (%32) idi, trombositopeni ise en az görülen laboratuvar bulgusuydu. Tedavi rejimlerine yönelik analizde en yaygın kullanılan tedavi doksisiklin ve rifampisindi. Başlangıçta yatan hastalarda aminoglikozid tedavisinin (%80) tercih edildiği fakat ayaktan hastalarda bu tedavi yönteminin yaygın olarak tercih edilmediği belirlendi. Tüm hastalar içinde sadece iki hastada hastalığın tekrarladığı görüldü. Tedavi yöntemleri ile hastalık nüksü arasında istatistiksel olarak anlamlı bir ilişki tespit edilmedi.
Sonuç: Ülkemizde her yıl binlerce çocuk eklem ağrısı şikayetiyle pediatri kliniklerine başvurmaktadır ve bu hastalar genellikle kapsamlı tetkikler ve anamnez ile incelenir. Ancak unutulmamalıdır ki, şüpheli hasta öyküsü ve demografi ile karaciğer enzimlerinde yükselme ve sitopeninin eşlik ettiği semptomların altında bruselloz olabilir.

Anahtar Kelimeler: Bruselosis, Süt ürünleri, Karaciğer enzimleri

Introduction

Brucella is relatively common in our country, especially in rural areas and in areas where the population involved in agriculture. The disease is spread by direct contact with the secretions of animals or through contaminated milk. Brucella is an animal-borne disease that threatens animal and human health. The Brucella bacterium is a Gram-negative aerobic coccobacillus according to the microbiological definition. In livestock, the type found in sheep is called B. melinentis and the type found in cattle is called B. abortus.[1] In children, there is a wide clinical variety. Common symptoms include musculoskeletal pain and loss of appetite and weight, leading to a general deterioration. In the diagnosis, the history of the family

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - iThenticate
Complaints: geneltip@selcuk.edu.tr

Selcuk University Press
Genel Tıp Dergisi | e-ISSN: 2602-3741
https://dergipark.org.tr/tr/pub/geneltip
https://yayinevi.selcuk.edu.tr/

and the living environment play the main role. The situation that should stand out in the history is that there is a similar history in the family or that the family is involved in farming and animal husbandry. Apart from this situation, of course, people who are not involved in animal husbandry can also get infected with brucella. People who use fresh dairy products from farmers' markets are at risk because they are not pasteurized. After making the diagnosis based on the medical history, we mainly use the parameters of the CBC as initial tests.[2] Anemia, leukopenia and thrombocytopenia can be detected, which can develop into pancytopenia. Antibiotics are used for the treatment and their effectiveness has been proven for years. The recommended duration of treatment and the use of appropriate dosage reduce the incidence of relapses and complications. Most patients recover without sequelae with combined antibiotic therapy. In rare cases, relapse occurs despite appropriate treatment. We collected patient data from the centers involved in the study, including patient demographic and clinical characteristics, and investigated whether there was a difference in outcomes between the different centers in our country.

Material and Methods

The records of patients treated as outpatients or inpatients with the diagnosis of brucellosis at our participating centers between October 2018 and December 2020 were scanned. We define the definitive diagnosis of the disease as Wright agglutination titer ≥1/160 or production of the agent in culture. Laboratory results along with the demographic characteristics of the patients were recorded in the system. Patients with low hb <10 g/dL, WBC <5000/mm³, PLT 150.000/mm were defined as pancytopenia. Recurrence was defined as 2 mercaptoethanol (2-ME) agglutination titers increase in addition to the development of symptoms again in the patient group whose treatment was completed.

Statistical analysis

The SPSS program (version 26.0, IBM Company, SPSS Inc) was used for statistical analysis. Descriptive statistics such as mean±standard deviation (SD), median, and range (smallest value-maximum value) depending on whether the data were parametric or not, as well as frequency (n) and percentage (%) for categorical variables, were used in determining the baseline characteristics of the participants. Normality of the distribution of continuous variables was assessed with the Shapiro-Wilks test. Comparison was made with the independent-samples t test if the normality assumption was met, otherwise with the nonparametric Mann-Whitney U test. Categorical data were compared with the chi-square test. Cases with a type 1 error level below 5% were interpreted as statistically significant.

Results

In our study, 48 patients met the criteria. Thirty-two of these patients were male (70%). The mean age of the group was (±SD) 9.8±3.3. It was found that 85% of the families of these patients consumed unpasteurized milk and 70% of them lived in rural areas. When the frequency of brucellosis in the families was investigated, it was determined that there was a family history in about half of the patients. When we ranked the symptoms by frequency, it was established that joint pain was the most important symptom at 75%. When we sorted the time of onset of the symptoms by season, it showed that they were most common in the spring and fall months with 30%. Evaluation of the laboratory results revealed a mean (±SD) total leukocyte count of 7,700±2,608/mm³, a neutrophil count of 3,500±2,106/mm³, a lymphocyte count of 3,409±1,404/mm³, and a PLT count of 270,308±64,104/mm³. Examination of the patients' hemograms revealed leukopenia in two patients, anemia in one patient, and thrombocytopenia in one patient. In the results, ALT values were high in 20% of the patients while AST elevations was less frequent. Liver enzyme levels and acute phase reactants are summarized in the tables.

Table1-Comparing Hospitalized and Outpatients groups

	Hospitalized (n=16)	Outpatient (21)	P*
WBC (/mm³)	7665 (3796-14584)	6602 (4941-12336)	0.973
Neutrophils (/mm³)	2531 (1164-11634)	3086 (1794-7924)	0.800
Lymphocytes (/mm³)	3530±1522	3487±1408	0.919
Monocytes (/mm³)	541 (300-1102)	516 (200-972)	0.932
Eosinophil (/mm³)	15 (0-130)	111 (11-830)	0.379
Platelets (/mm³)	264658±72825	284242±63195	0.378
CRP (mg/dl)	6.43 (3.06-112.3)	3.24 (3.06-33.2)	0.913
ESR (mm/h)	17.5(4.08-55.2)	17.2 (2.4-40.8)	0.314
Aminoglycosides	13 (81.4%)	6 (24.7%)	0.001
Relapse	1 (6.24%)	3 (14.5%)	-

WBC, white blood cell; **CRP**, C-reactive protein; **ESR**, erythrocyte sedimentation rate. * Mann-Whitney U or t-test or Chi-Square

There was no statistically significant difference between laboratory values of outpatients and inpatients (p > 0.050). Rose Bengal test and agglutination test were positive in serum of all patients. Brucella agglutination titers ranged from 1/160 to 1/10240. Twenty (54%) patients were admitted as inpatients and received further treatment. Brucella melitensis was isolated from blood cultures of three (15%) hospitalized patients. It was also isolated in the joint fluid culture of a patient with arthritis and in the bone marrow culture of a patient who underwent bone marrow aspiration due to bictopenia. Sixteen (43.2%) cases were treated with doxycycline plus rifampicin, 12 (30.6 %) with doxycycline plus rifampicin plus gentamicin, 8 (19.8%) with trimethoprim/sulfamethoxazole plus rifampicin plus gentamicin, and 4 (9.1%) with trimethoprim-sulfamethoxazole plus rifampicin. The addition of aminoglycoside to initial therapy was statistically higher in hospitalized patients than in outpatients (80.1% vs. 22.9%) (p=0.001). The overall aminoglycoside utilization

rate was 48.6%. During follow-up, relapse occurred in 5 (11.7%) cases, 4 of which were outpatients, and in all cases, treatment was either not administrated regularly or discontinued prematurely. All these cases received 6 weeks of combined triple therapy, including aminoglycosides in the first 2 weeks according to age. There was no statistical association between the initial treatment regimen and relapse (p=0.413). One of our patients developed hemophagocytic lymphohistiocytosis (HLH) during follow-up, and one of our patients was diagnosed with neurobrucellosis although no mortality was observed.

Discussion

The significant characteristics of our research revealed that joint pain frequency, mild leukopenia, thrombocytopenia, and male gender were the most prominent features of brucellosis.

Table 2. Symptomology

Pub.	Fever%	Arthritis%	Joint Pain%
Büyükçam et al.	12	21	67
Çiftdoğan et al.	78	23	79
Bayhan et al.	82	70	77
Özcanaslan et al.	94	24	76
Our Results	20	21	80

Brucellosis is prevalent amongst children in developing countries due to unpasteurized milk and livestock. [1,2]It is an endemic zoonotic disease in our country, affecting individuals of all ages and genders. However, younger than 14 years individuals account for 11-56% of patients with brucellosis in endemic regions. In 18 studies conducted in our country from 2011 onwards, which focused on children over 18 years of age, the average age ranged from 7.3 to 11.9 years.[3]

Table3. Results from Turkish Studies.

Pub.	N	Family History%	Unpasteurized Milk.%
Karaman et al.	73	28	91
Özcanaslan et al.	65	38	93
Our Results	37	49	87

The male cases were generally between 30-69.3% according to the reports, except for three studies that reported this rate as 45-46.8%. In 15 studies, a male predominance was observed with rates ranging from 54.4-75%.[4] Hematologic complications, including anemia, leukopenia, and thrombocytopenia, are commonly observed during brucellosis, while pancytopenia is less frequently seen. During acute brucellosis cases and in patients with growth in blood culture, hematologic complications such as anemia, leukopenia, and thrombocytopenia are more commonly observed than in recurrent cases. However, these complications are generally mild and can be resolved quickly with antimicrobial therapy.[5] In rare cases, thrombocytopenia can be severe and lead to skin and mucous membrane bleeding. Studies on hematologic findings have reported varying rates of leukopenia, thrombocytopenia and pancytopenia. If patients in endemic areas are diagnosed with immune thrombocytopenic purpura and pancytopenia, brucellosis should be considered at the time of diagnosis. However, because pancytopenia is a rare finding, other potential causes such as leukemia, should also be taken into account.[6] The lower rates of leukopenia and thrombocytopenia in our study may be related to the lower rate of bacteremia among our patients. Although most patients with brucellosis have normal or slightly elevated aminotransferase levels, the liver, which is the largest organ of the reticuloendothelial system, is always affected in brucellosis. In rare cases, acute hepatitis may occur with aminotransferase levels resembling viral hepatitis. In our country, only four studies have reported brucellosis-related hepatitis. These studies showed lower rates of transaminase elevation compared to international studies. We suspect that this may be due to the early diagnosis of Brucella, which is endemic in our country. As a result, the liver damage may not have progressed enough to cause significant increases in aminotransferase levels.[7] The rates of transaminase elevation reported in our country are 17.3%-54.6. Antimicrobial therapy is important for reducing morbidity, shortening the duration of the disease, and preventing complications associated with brucellosis. Long-term treatment is necessary for complete recovery. Combination therapy with two or more antibiotics is recommended to reduce the risk of relapse, which is high with monotherapy. In children, doxycycline plus rifampicin is typically used for those older than 8 years while trimethoprim-sulfamethoxazole plus rifampicin is used for those younger than 8 years for at least 6 weeks. Aminoglycosides such as gentamicin can be added to the treatment regimen for severe infections to increase bacterial killing. Studies conducted in our country showed a varying preference rate for aminoglycosides in treatment, ranging from 1.3% to 93.9% while international studies reported a rate of 100%. Most patients with brucellosis recover completely after receiving appropriate treatment. Despite receiving appropriate treatment, some patients may experience relapses, usually within the first six months of therapy. The cause of relapse is usually due to early discontinuation of treatment rather than drug resistance, and triple therapy is recommended for relapsed cases.[8] In studies conducted in our country, the reported relapse rates range from 1.3% to 7.9%, while international studies that use dual treatment regimens with aminoglycosides report a higher relapse rate of 20% to 31%. To improve treatment outcomes, pediatricians should educate patients and their families on how to adhere to the prescribed antibiotic regimens and conduct long-term follow-up evaluations. Our observation suggests that hospitalized patients have a lower relapse rate, but statistical analysis could not be performed due to the small number of patients. The authors of the study

observed a lower relapse rate in hospitalized pediatric patients with brucellosis compared to outpatient cases, and attributed this to increased treatment adherence due to the severity of the disease requiring hospitalization. They suggested that initiating inpatient treatment and closely monitoring treatment could potentially increase treatment adherence and reduce relapse rates.

Limitations

The study has limitations due to its retrospective design and the relatively small number of patients included.

Conclusion

Brucellosis is a significant health concern in Türkiye that can result in severe health consequences for individuals. It is crucial for healthcare professionals to consider brucellosis in their differential diagnosis for patients presenting with symptoms such as joint pain, cytopenia, and elevated aminotransferase levels, and to conduct family screening when a family member is diagnosed with brucellosis. Furthermore, improving treatment adherence is critical in reducing the risk of relapse, and developing new strategies to improve adherence during the lengthy treatment period is imperative. It should be noted that our study has limitations due to its retrospective design and relatively small sample size of patients.

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