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Fever of Unknown Origin in Children: A Single Center Experience from Southern Türkiye

Çocuklarda Nedeni Bilinmeyen Ateş: Türkiye'nin Güneyinden Tek Merkez Deneyimi

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Abstract

Objective: It is aimed to determine the etiology, clinical features and short-term prognosis in pediatric patients with fever of unknown origin (FUO). The study included patients with a history of fever lasting more than a week with a fever >38.3 °C despite being hospitalized for eight days and more or examined in the outpatient clinic.

Material and Methods: Study is performed in Adana City Training and Research Hospital between January 2018-September 2021. Patients' diseases were investigated in four groups according to etiological causes, including infectious diseases, non-infectious inflammatory diseases, malignant diseases and others.

Results: Of 65 patients, 34% were female, 66% were male. Forty percent of the patients had infectious diseases, while 33.8% were included in the non-infectious inflammatory diseases group. Sixteen point nine percent of patients had malignant diseases. The most common infectious disease was tuberculosis (23%), the most common non-infectious inflammatory disease was juvenile idiopathic arthritis (JIA) (20%) and leukemia (9.1%). The shortest mean time of diagnosis was 10 days for infectious diseases. The group with the least antipyretic response was the malignant group (27%). Invasive examinations aided the diagnosis of diseases with a rate of 37%.

Conclusion: Despite advanced diagnostic tests and increasing clinical experience, FUO is a disease that remains uppermost important, and infectious diseases rank first among the causes of FUO.

Keywords: Child, fever, infection

Öz

Giriş: Bu çalışmada, nedeni bilinmeyen ateşi (NBA) olan pediyatrik hastalarda etiyolojinin, klinik özelliklerin ve kısa dönem prognozun belirlenmesi amaçlanmaktadır. Çalışmaya, sekiz gün ve daha uzun süre hastanede yatan veya poliklinikte muayene olan ancak ateşi >38.3 °C olan ve bir haftadan uzun süren ateş öyküsü olan hastalar dahil edildi.

Gereç ve Yöntemler: Çalışma Ocak 2018-Eylül 2021 tarihleri arasında Adana Şehir Eğitim ve Araştırma Hastanesinde yapılmıştır. Hastaların hastalıkları etiyolojik nedenlere göre enfeksiyon hastalıkları, enfeksiyon dışı enflamatuvar hastalıklar, malign hastalıklar ve diğerleri olmak üzere dört grupta incelenmiştir.

Bulgular: Altmış beş hastanın %34'ü kız, %66'sı erkekti. Hastaların %40'ında enfeksiyon hastalıkları mevcutken, %33.8'i enfeksiyon dışı enflamatuvar hastalıklar grubuna dahil edildi. Hastaların %16.9'unda malign hastalık vardı. En sık görülen enfeksiyon hastalığı tüberküloz (%23) iken, en sık görülen enfeksiyon dışı enflamatuvar hastalık juvenil idiyopatik artrit (JİA) (%20) ve lösemidir (%9.1). Enfeksiyon hastalıklarında ortalama tanı süresi 10 gündür. Antipiretik yanıtın en az olduğu grup ise malign gruptur (%27). İnvaziv muayeneler hastalıkların tanısına %37 oranında yardımcı olmuştur.

Sonuç: NBA, gelişmiş tanı testlerine ve artan klinik deneyime rağmen önemini koruyan bir hastalıktır ve NBA nedenleri arasında enfeksiyon hastalıkları ilk sırada yer almaktadır.

Anahtar Kelimeler: Çocuk, ateş, enfeksiyon

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Introduction

While fever is a very common finding in children, fever of unknown origin (FUO) is seen less frequently (1). Petersdorf and Beeson first defined this concept in 1961 for clinical cases characterized by a fever exceeding rectal 38.3 °C (101 °F) persisting for a minimum of three weeks, and for which the cause remained undisclosed despite investigations conducted in the hospital for one week (1). While this definition remains in use, especially in children, there is no universally accepted standard view. Despite advancements in diagnostic tests and increased clinical experience, this issue holds paramount importance worldwide and remains open to further research. The most recent definition in children associated with a rectal fever persisting above 38.3 °C for a duration of eight days or longer, whether the patient is hospitalized or receiving outpatient care, with no apparent cause determined despite physical examinations and initial laboratory tests (2). However, it is widely acknowledged that infectious diseases, collagen tissue disorders, inflammatory diseases, malignant conditions, and other illnesses are among the most common contributors to FUO (3-6). The specific infectious agents involved may vary based on the region, the type of healthcare facility, and the prevailing endemic factors. Notably, the proportion of non-infectious inflammatory diseases in the etiology of FUO tends to be higher, particularly in developed and Asian countries (7,8). A study focused on pediatrics has underscored the significance of age in this context, revealing that the likelihood of infectious diseases as the etiology decreases with age, while collagen vascular diseases become more prevalent in individuals older than three years of age (9). In this study, it is aimed to investigate demographic, clinical characteristics, laboratory values, complications of the children diagnosed with FUO who were followed up in our clinic and to determine their short-term prognosis.

Materials and Methods

Study Population

Our clinic is a third-level reference hospital with 134 pediatric and 30 intensive care beds. Patient selection; between January 1, 2018, and September 30, 2021, patients with a history of fever lasting more than one week with >38.3 °C (rectal) despite being hospitalized for eight days or more or being treated in the outpatient clinic in Adana City Training and Research Hospital Pediatrics Clinic Patients were included. The patients' ages varied between one month and 18 years and they were diagnosed with persistent fever and fever of unknown origin and followed up.

Exclusion Criteria

This encompassed the following groups: Newborn patients aged 0-28 days, patients with a documented history of immunocompromised diseases, patients with a confirmed diagnosis of malignancy, patients who presented to our center with prolonged fever and received initial diagnoses of various diseases (e.g., brucellosis, Kawasaki disease), individuals diagnosed with multisystem inflammatory syndrome in children (MIS-C), and patients with undetermined diagnoses.

Data Collection

Demographic, clinical characteristics, examinations, complications and short-term prognosis of the patients were recorded through daily physical examination and repeated anamnesis. Patients were divided into four groups; infectious diseases, collagen tissue, autoimmune and inflammatory diseases, malignant diseases and others. The examinations performed were grouped as primary and secondary examinations. First-line laboratory tests, such as complete blood count, blood smear, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), procalcitonin, liver function tests and kidney function tests, electrolytes, ferritin, lactate dehydrogenase (LDH), albumin, fibrinogen, complete urinalysis, blood/urine culture, chest X-ray and tuberculin skin test was recorded. Second-line examinations consisted of serological tests, acid-fast bacillus (ARB) in sputum, sputum culture, stool culture, immunoglobulins, rheumatological markers, oncological markers, imaging methods [ultrasonography (USG), echocardiography (ECHO), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET/CT)], invasive methods (skin, lymph node, brain and tissue biopsy, bone marrow aspiration/biopsy, endoscopy, colonoscopy) and genetic examination.

Definitions

In diagnosing infectious diseases, in addition to clinical findings, laboratory methods of infectious disease such as *Brucella* diagnosis, blood culture and Coombs titration above 1/160 were also accepted as disease positivity. Tuberculosis (TB) diagnosis-pulmonary TB; mycobacteria positivity and culture positivity in ARB in sputum, extrapulmonary TB diagnosis through contact history was established via imaging methods, cerebrospinal fluid sample and lymph node biopsy sample. The diagnosis of leishmania was made with the presence of amastigote in the bone marrow and antigen positivity. Serological and PCR methods and viral DNA measurement diagnosed viral infections. Infective endocarditis was diagnosed by according to modified Duke criteria. The diagnosis of hemophagocytic lymphohistiocytosis was based on diagnostic criteria like bone marrow findings and genetic diagnosis. Diagnosis of malignant diseases was made by invasive methods, imaging methods, clinical findings and histopathology. Collagen tissue and inflammatory diseases were diagnosed with genetic tests, imaging methods and invasive examinations. Especially in clinically compatible patients, the diagnosis of JIA was made by excluding other diseases.

Data Analysis

Categorical measurements were summarized as numbers and percentages, and numerical measurements were summarized as mean and standard deviation (median and IQR: Inter quartile range: 75^{th}-25^{th} percentile where appropriate). Chi-square test statistics were used to compare categorical measures between groups. Bonferroni-corrected Z-test was used for pairwise comparisons of the groups for the cases found to be significant in these analyses. The Shapiro-Wilk test tested whether numerical measurements provided the assumption of normal distribution. In the general comparison of the numerical measurements of the groups, a one-way analysis of variance was used if the assumptions were met and the Kruskal Wallis test was used if the assumptions were not met. For the cases found significant in these comparisons, Gabriel, Hochberg GT2 and Games-Howell tests were used according to whether the in-group variances were homogeneous or if the assumptions were met in pairwise comparisons of the groups. If the assumptions were not met in pairwise comparisons of the groups, the Mann-Whitney U test with Bonferroni correction was used. IBM SPSS Statistics Version 20.0 package program was used to analyze the data. The statistical significance level was accepted as 0.05 in all tests. Pairwise comparisons of the groups (a: $p< 0.05$ for infection vs. malignancy, b: $p< 0.05$ for infection vs. vascular-autoimmune, c: $p< 0.05$ for infection vs. other, d: $p< 0.05$ for malignancy vs. vascular-autoimmune, e: It was stated as $p< 0.05$ for malignancy vs. other, f: $p< 0.05$ for vascular-autoimmune vs. other).

Ethics committee approval was received for the study at the meeting of Adana City Training and Research Hospital Clinical Research Ethics Committee dated 14.10.2021 (Meeting No. 90; Decision No. 1597).

Results

Of the 65 patients followed and diagnosed with FUO, 42 (65%) were Turkish citizens and 23 (35%) were immigrants. Of all patients, 34% were female and 66% were male. The mean age was 107.6 ± 65.5 months, and highest in the infectious diseases group. When the patient age groups are divided into four groups; 1-23 months, 24-71 months, 72-143 months and over 144 months, the highest rate of patients over the age of 12 was in infectious diseases, followed by non-infectious inflammatory diseases (Table 1).

In our study, 26 patients (40%) had infectious diseases; tuberculosis (15/65, 23.2%, pulmonary four cases, extrapulmonary 11 cases), zoonotic diseases (7/65, 10.7%, leishmania three cases, brucellosis two cases, toxoplasmosis one case and bartonellosis one case), viral diseases [3/65, 4.6%, cytomegalovirus (CMV) two cases, Epstein-Barr virus (EBV) one case] were in the other infectious diseases group (1/65, 1.5% was infective endocarditis). Twenty two patients (33.8%) were in the group of non-infectious inflammatory diseases, 11 patients (16.9%) were in the group of malignant diseases and 6 patients (9.3%) were in the group of other diseases. The diseases that consisted of these groups are given in Table 2.

In our study, the shortest diagnosis duration was observed in infectious diseases (average 10 days) and the longest in the diagnosis group of other diseases (mean 20 days). Malignant diseases were the group with the most prolonged mean duration of total fever of 70 days (minimum-maximum: 55-80) and the least (27%) response to antipyretics (Table 1). Non-response to antipyretics in the patients was 22/65, 33.8%. Unresponsiveness to antipyretics in infectious diseases (3/26, 11.6%, miliary TB two cases, abdominal TB one case), non-infectious inflammatory diseases [5/22, 22.7% JIA four cases, poliarteritis nodosa (PAN) one case], malignant diseases [8/11 cases, 72.7%, acute lymphocytic leukemia (ALL) four cases, Hodgkin lymphoma three cases, Primitive neuro-ectodermal tumor (PNET) one case], in the other diseases group (6/6, 100%, hemophagocytic lymphohistiocytosis four cases, combined immunodeficiency one case, Crisponi syndrome one case).

While all of the patients had a history of fever, other findings were as follows; abdominal tenderness in 32 (49%), hepatomegaly 20 (30.7%), rash 20 (30.7%), joint range of motion restriction in 19 (29.2%), splenomegaly 18 (27.6%), lymphadenopathy in 17 patients (26.1%) (Table 1). In infectious diseases, abdominal tenderness was detected in 11 (42%), rales in 9 (35%), lymphadenopathy in 9 (35%), and hepatomegaly in 8 (31%) patients. Rales and conjunctivitis were more common in infectious diseases than in all other groups. In malignant diseases, abdominal tenderness was detected in 7 (64%) patients, hepatomegaly in 6 (55%), and lymphadenopathy in 4 (36%) patients. Abdominal tenderness, hepatomegaly and lymphadenopathy were more common in malignant diseases than in all other groups. In collagen tissue, autoimmune and inflammatory diseases, physical examination revealed joint movement limitation in 13 (59%) patients, rash in 12 (55%), abdominal tenderness in 11 (50%), and joint swelling in 9 (41%) patients. The incidence of swelling and limitation of movement in the joint was higher in the collagen tissue and inflammatory disease group than in all other groups ($p= 0.005^{b,d,f}$, $p< 0.001^{b,d,f}$). The incidence of rash was higher in the collagen tissue and inflammatory disease group than in the infection and malignancy group ($p= 0.005^{b,d}$).

When the first step laboratory tests were examined, it was observed that the white blood cell (WBC) value and the neutrophil value were lower in the infection group than in the collagen tissue, autoimmune and inflammatory disease group and other diseases diagnosis group, respectively ($p= 0.002^{b,c}$, $p< 0.001^{b,c}$). The mean hemoglobin value was lower in the malignant disease group than in all other groups ($p= 0.017^{a}$). The mean CRP value was the lowest in

Table 1. Demographic, fever and patient characteristics according to the diagnosis groups of the patients

		Diagnostic Groups				
		Infection Diseases n= 26	**Malignant Diseases n= 11**	**Non-infectious Inflammatory Diseases n= 22**	**Other Diseases n= 6**	**p**
Nationality, n (%)						
Türkiye	42/65 (65%)	17 (65%)	5 (45%)	17 (77%)	3 (50%)	
Syria	23/65 (35%)	9 (35%)	**6 (55%)**	5 (23%)	3 (50%)	0.267
Gender, n (%)						
Female	22/65 (34%)	13 (50%)	3 (27%)	5 (23%)	1 (17%)	
Male	43/65 (66%)	13 (50%)	**8 (73%)**	**17 (77%)**	**5 (83%)**	0.175
Age, mean ± SD, median (IQR)		**107.6 ± 65.5** 131 (131)	88.3 ± 50.6 85 (66)	104.5 ± 69.0 90 (135)	32.2 ± 25.5 33.5 (45)	0.091
Age groups, n (%)						
1-23 months		3 (12%)	1 (9%)	3 (13%)	2 (33%)	
24-71 months		7 (27%)	4 (36%)	5 (23%)	3 (50%)	
72-143 months		4 (15%)	5 (46%)	5 (23%)	1 (17%)	
144-216 months		**12 (46%)**	1 (9%)	9 (41%)	0 (0%)	0.176
Diagnosis duration		10 (8-12)	13 (12-15)	11 (10-14)	20 (14-20)	**0.005**[c]
Fever duration		45 (40-75)	70 (55-80)	50 (45-65)	45 (45-50)	0.094
Antipyretic response		23 (88%)	3 (27%)	22 (100%)	6 (100%)	**<0.001**[a]
Examination finding/Number of patients examined						
Tenderness in the abdomen	32/65	11 (42%)	7 (64%)	11 (50%)	3 (50%)	0.731
Hepatomegaly	20/65	8 (31%)	6 (55%)	3 (14%)	3 (50%)	0.059
Rash	20/65	4 (15%)	1 (9%)	12 (55%)	3 (50%)	**0.005**[b,d,f]
Joint range of motion	19/65	2 (8%)	4 (36%)	13 (59%)	0 (0%)	**<0.001**[b,d,f]
Splenomegaly	18/65	8 (31%)	2 (18%)	6 (27%)	2 (33%)	0.871
Lymphadenopathy	17/65	9 (35%)	4 (36%)	3 (14%)	1 (17%)	0.295
Ral	16/65	9 (35%)	2 (18%)	3 (14%)	2 (33%)	0.338
Swelling in the joint	11/65	2 (8%)	0 (0%)	9 (41%)	0 (0%)	**0.005**[b,d,f]

Mean ± SD: Mean ± standard deviation, Median (IQR): Median (75th percentile-25th percentile).
a= p< 0.05 for infection vs. malignancy, b= p< 0.05 for infection vs. vascular-autoimmune, c= p< 0.05 for infection vs. other, d= p< 0.05 for malignancy vs. vascular-autoimmune, e= p< 0.05 for malignancy vs. other, f= p< 0.05 for vascular-autoimmune vs. other.

infectious diseases and was statistically significant (p< 0.001[b]). Furthermore, the mean ESR, ferritin and fibrinogen values were lower in the infection group than in all groups, respectively (p< 0.001[b], p= 0.001[b], p< 0.001[b]). Although non-blood primary care tests are necessary and instructive, no significant difference was observed among groups (Table 3).

In the second step examinations; serological tests, USG and ECHO from imaging methods and bone marrow biopsy among invasive tests were the most frequently used. CT was used from 48 (74%) patients and symptoms were detected in 28 (43%) patients. The rate of patients with CT findings in the infection group was higher than in the other groups (p= 0.001[a,b,c]). In 9 (100%) of nine patients who underwent PET/CT, the focus of inflammation was demonstrated. Although it is an essential test, it could not be evaluated statistically. The etiology of fever (miliary TB, Hodgkin lymphoma and PNET metastasis) was verified in 6 (66%) of these patients (Table 3).

Invasive investigations helped the diagnosis in 24 (37%) of 65 patients. The rate of patients with significant findings in bone marrow biopsy in the collagen tissue and inflammatory group was lower than in the other groups (p< 0.001[b,d,f]). Biopsy was performed on 16 (24.6%) patients, 14 (21.5%) lymph node biopsies, 2 (3%) skin biopsies. It was observed that the rate of patients with biopsy findings in the infection and malignancy groups was higher than in the other groups (p= 0.008[b,c,d,e]) (Table 3).

Genetic analyzes were requested from 26 patients and symptoms were detected in 13 patients. However, there was no statistically significant difference among the groups. These analyzes aided the diagnosis of periodic

Table 2. Diagnoses made in patients with fever of unknown origin

Diagnosis	Cases, n	(%)
Infectious Diseases	**26**	**40.0**
Tuberculosis	**15**	**23.2**
Pulmonary tuberculosis	4	6.3
Extrapulmonary tuberculosis		
Tuberculous meningitis	3	4.6
Tuberculous lymphadenitis	3	4.6
Miliary tuberculosis	3	4.6
Abdominal tuberculosis	2	3.1
Zoonotic Diseases	**7**	**10.7**
Leishmania	3	4.6
Brucella	2	3.1
Toxoplasma	1	1.5
Bartonella	1	1.5
Viral Diseases	**3**	**4.6**
Cytomegalovirus	2	3.1
Epstein-Barr virus	1	1.5
Others	**1**	**1.5**
Infective endocarditis	1	1.5
Non-infectious Inflammatory Diseases	**22**	**33.8**
Juvenile idiopathic arthritis	13	20.0
Familial mediterranean fever	4	6.2
Crohn's disease	3	4.6
Polyarteritis nodosa	1	1.5
Infantile kawasaki	1	1.5
Malignant Diseases	**11**	**16.9**
Leukemia		
Acute lymphoblastic leukemia	5	7.6
Acute myeloid leukemia	1	1.5
Hodgkin lymphoma	4	6.3
Primitive neuroectodermal tumor	1	1.5
Other Diseases	**6**	**9.3**
Hemophagocytic lymphohistiocytosis	4	6.3
Common variable immunodeficiency	1	1.5
Crisponi syndrome	1	1.5

fever syndromes, hemophagocytic lymphohistiocytosis and Crisponi syndrome.

Treatment protocols were initiated following the diagnoses of the patients. During the follow-up, sequelae were found in 7 (11%) patients. Gait disturbance in five of the patients (7.7%) (these were patients with miliary TB, TB meningitis, CMV, JIA, leukemia), 1 (TB meningitis) hydrocephalus needed a ventriculoperitoneal shunt and 1 (PAN) left hand 3-4 phalanx necrosis and autoamputation were observed. Two patients diagnosed with FUO died during the six-month follow-up period. These patients were in malignancy group diseases and diagnosed with acute myeloid leukemia and primitive neuroectodermal tumor metastasis.

Since the date range in which the study was conducted coincided with the COVID-19 pandemic, the cases were divided into two as the period before and after the date of the first COVID-19 case in our country, and the etiological factors of the patients are given in Table 4 according to the periods. When the etiological reasons were examined in detail, no significant difference was seen between the two periods.

Discussion

This study determined the etiology of FUO and the results noted that infectious diseases ranked first as the primary cause. Additionally, the most common cause of FUO was tuberculosis. Examining studies evaluating pediatric patients

Table 3. Diagnostic evaluation: Consults, imaging, and laboratory studies

		Diagnostic Groups				
		Infection Diseases n= 26	**Malignant Diseases n= 11**	**Non-infectious Inflammatory Diseases n= 22**	**Other Diseases n= 6**	**p**
Primary Care Examinations						
White blood cell (mcL)		8.650 (5.700-12.800)	8.700 (4.900-12.100)	15.550 (11.600-19.700)	9.500 (31.00-13.900)	**0.002[b,c]**
Neutrophil (mcL)		4.300 (2.900-7.600)	3.600 (2.100-4.640)	10.150 (8.100-15.600)	5.650 (1.200-9.600)	**<0.001[b,c]**
Hemoglobin (gr/dL)		10.6 ± 1.7	8.6 ± 2.3	9.5 ± 1.9	8.8 ± 2	**0.017[a]**
C-reactive protein (mg/L)		20.7 (7.6-67)	128 (28-241)	158 (120-200)	84.5 (24.8-151)	**<0.001[b]**
Sedimentation (mm/h)		30 ± 19.4	62.2 ± 27.9	68.2 ± 31.6	52.2 ± 25.9	**<0.001[a,b,c]**
Ferritin (µg/L)		68 (23-140)	244 (159-355)	398 (100-1686)	733.5 (180-1877)	**0.001[a,b,c]**
Fibrinogen (mg/dL)		309.3 ± 138.3	555.4 ± 231.7	584.1 ± 145	413 ± 201.6	**<0.001[a,b,c]**
Second line examinations significant finding/Number of patients examined						
Serology	10/65	6 (23%)	1 (9%)	1 (5%)	2 (33%)	0.137
Echocardiography	13/65	2 (8%)	2 (18%)	6 (27%)	3 (50%)	0.066
Ultrasonography	32/65	12 (46%)	7 (64%)	9 (41%)	4 (67%)	0.526
Immunoglobulins	7/65	3 (12%)	1 (9%)	1 (5%)	2 (33%)	0.256
Oncological markers	1/59	0 (0%)	0 (0%)	1 (6%)	0 (0%)	0.593
Rheumatological markers	10/48	2 (15%)	1 (13%)	6 (27%)	1 (20%)	0.865
Computed tomography	28/46	18 (90%)	4 (44%)	6 (43%)	0 (0%)	**0.001[a,b,c]**
Bone marrow	16/46	4 (33%)	8 (73%)	0 (0%)	4 (67%)	**<0.001[b,d,f]**
Magnetic resonance	15/40	7 (47%)	3 (43%)	5 (31%)	0 (0%)	0.664
Acid-fast bacillus	2/33	1 (5%)	0 (0%)	0 (0%)	1 (33%)	0.261
Sputum culture	1/26	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0.346
Genetic testing	14/26	2 (29%)	1 (100%)	7 (43%)	4 (100%)	0,065
Biopsy	14/16	10 (100%)	4 (100%)	0 (0%)	0 (0%)	**0.008[b,c,d,e]**
Stool culture	1/15	0 (0%)	0 (0%)	1 (12,5%)	0 (0%)	0.999
Leishmania dipstick	3/13	3 (50%)	0 (0%)	0 (0%)	0 (0%)	0.497
PET/CT	9/9	2 (100%)	6 (100%)	1 (100%)	0 (0%)	---**
Endoscopy	2/6	0 (0%)	0 (0%)	2 (40%)	0 (0%)	0.999
Colonoscopy	4/5	0 (0%)	0 (0%)	4 (100%)	0 (0%)	0.200

Here, percentages were calculated by excluding those who did not have a test result. Accordingly, comparisons were made.
**There was no normal finding among those performed as a result of scintigraphy/PET. Therefore, comparisons could not be made here.
a: p< 0.05 for infection vs malignancy, b: p< 0.05 for infection vs. vascular-autoimmune, c: p< 0.05 for infection vs. other, d: p< 0.05 for malignancy vs. vascular-autoimmune, e: p< 0.05 for malignancy vs. other, f: p< 0.05 for vascular-autoimmune vs. other.

revealed that the most common etiology is infectious diseases in Türkiye and international studies (3-6,10-13) (Table 5). Although the rate of non-infectious inflammatory diseases was reported to increase in studies conducted on adults and children worldwide, it is still shown as the most common cause is infectious diseases (7,14). The most common cause of infectious diseases in developed countries are viral infections, while in developing countries they are bacterial infections (2). In the current study, the most common cause of infectious diseases was tuberculosis, followed by leishmania and *Brucella* from zoonotic diseases. Therefore, the importance of geographical effect and being an endemic region was seen in the frequency of infectious causes. Tuberculosis is still the most common cause of FUO as a critical infectious agent worldwide.

Table 4. Admission numbers before and after COVID-19 period

Etiological Factor	Before March 2020	After March 2020	Total Number
Infectious	14	12	26
Hematological	5	6	11
Rheumatological	11	11	22
Others	1	5	6
Total Number	31	34	65

Table 5. Diagnoses made in patients with fever of unknown origin

Diagnosis	Chow (2011) n= 1638	Chien (2017) n= 79	Antoon (2018) n= 102	Xu (2022) n= 357	Çiftçi (2003) n= 102	Cogulu (2003) n= 80	Tezer (2012) n= 77	Gündeşlioğlu (2019) n= 30
Infectious diseases (%)	51	37.6	41.1	45.7	44.2	58	50	46.6
Collagen tissue autoimmune and inflammatory diseases (%)	9	14.0	**27.45**	**37.2**	6.8	6.25	7.2	**26.7**
Malignant diseases (%)	6	**17.2**	17.64	5.9	11.7	2.5	14	16.7
Other diseases (%)	11	16.1	13.81	11.2	**24.5**	12.5	**27**	3.3
Undiagnosed (%)	**23**	15.1		-	12.8	**20.75**	1.8	6.7

Likewise in our study, four cases pulmonary tuberculosis and 11 cases extrapulmonary (15/65, 23.2%) were detected. Also, infectious diseases were the primary cause in patients over 12 years. Vector-transmitted or zoonotic diseases have an important place in FUO; however, it was not possible to take the complete history of contamination among these patients, which provided a diagnostic problem.

In a study evaluating the distribution of gender in etiology, it was shown that infectious diseases were more common among male patients, while female patients were frequently diagnosed with collagen tissue diseases (6). A pediatric study revealed that the rate of infectious diseases in the etiology decreases with increasing age and collagen vascular disease is more common in those older than three years (9). In our study, the mean age and the rate of infectious diseases were found to be higher in patients over 12 years of age, which is consistent with studies in the literature. This explains that the detection of viral infections, especially in early childhood, is facilitated by progressive diagnostic tests and increasing experience and the reason why the most common cause of infectious diseases observed in the current study is tuberculosis.

In most of the studies, collagen tissue diseases are the second most common etiology and its rate in the etiology is increasing (5,6,10). Although malignant diseases generally have a rate of 10-20%, some studies included them as the second most frequent. Additionally, some studies included a group of other diseases and undiagnosed patients in the same group; therefore evaluating four main etiological groups (5). Finally, other studies in which undiagnosed patients were not included yet, still grouped patients into four main groups (6).

In our study, infectious diseases, collagen tissue and inflammatory diseases, malignant diseases and diseases forming the other group were followed most frequently, respectively. Undiagnosed patients were not included in the study and the etiology of the FUO was evaluated under four main groups. Although the results were similar to the ones observed in other studies, it was reported that collagen tissue, autoimmune and inflammatory group diseases increased proportionally. JIA was the most common among autoimmune and inflammatory diseases. On the other hand, acute lymphoblastic leukemia was the most common among malignant diseases and hemophagocytic lymphohistiocytosis was the most common among the diseases forming the other group.

It is commonly acknowledged that many studies referred to the duration of fever as stated in the standard definition, ranging from five days to three weeks. However, a recent review stated that it is more appropriate to express FUO despite first-line investigations rather than the duration of the fever (more than one week) in explaining the definition of FUO (7). In many studies, the duration of diagnosis is shortened, especially in infectious diseases, due to progressive diagnostic tests and increasing experience (6,15). In our study, following the literature, the shortest diagnosis time was seen in infectious diseases (mean: 10 days). The mean total fever duration and mean hospital stay in the malignant diseases group were longer than all other groups, while it also had the least (27%) response to antipyretics. Malignancy should always be kept in mind in resistant and long-lasting febrile diseases.

Primary and basic examinations reveal many diseases in the etiology of FUO. Therefore, it may provide clues for diagnosis. Followed by FUO studies evaluating reference laboratory tests in patients

examined, in one study, increased CRP levels were associated with infectious diseases and other diagnostic diseases (16). Hemoglobin value, one of the preliminary blood tests, was found to be lower in the malignant disease group than in the other groups, and it was found that the white blood cell value varied among the groups (16,17). In addition, ESR, ferritin, and fibrinogen values were lower in infectious diseases compared to collagen tissue, autoimmune and inflammatory disease groups, which is explained by the fact that infectious diseases are composed of diseases with a chronic course.

In a study evaluating imaging methods, X-ray, USG, CT, MRI, and PET/CT were noted as the most frequently applied examinations, respectively (18). In our study, the most frequently imaging modalities used were X-ray, USG, and ECHO, which were requested from all patients, followed by CT, MRI, PET/CT, respectively. CT was requested from a total of 48 (74%) patients, and symptoms were detected in 28 (43%) patients. However, the rate of patients with CT findings in the infection group was higher than in the other groups. This shows that the most common cause of infectious diseases is tuberculosis and that CT is an important imaging method for tuberculosis. Also with PET/CT, the focus of inflammation could be detected with a sensitivity of 90%, contributing to the diagnosis in 25-69% of patients (18). In another study, the cause of fever was determined by PET/CT in 53 (48%) of 110 patients (19), while in another one, it was detected in 82%, contributing to the diagnosis at a rate of 73% (20). In the current study, the focus of inflammation was shown in 9 (100%) of a total of nine patients who underwent PET/CT. In 6 (66%) of these patients, the etiology of fever was verified by PET/CT (miliary tuberculosis, Hodgkin lymphoma, and PNET metastasis).

Finally, when invasive examinations were evaluated, infections and collagen tissue disorders were frequently diagnosed with non-invasive examinations, while malignancy and other diseases constituting the group were frequently diagnosed with invasive interventions. Invasive examinations are helpful in the diagnosis process, with a rate of 43.7% (21). Likewise, invasive examinations helped diagnose 24 (37%) of 65 patients, while also diagnosed 23% of the patients in the other group, collagen tissue diseases in 23%, autoimmune and inflammatory diseases in 13%, malignant diseases in 100%, and 66% of the patients in the other group.

The etiology of FUO may vary depending on the endemic area of the study, socioeconomic conditions, the hospital's status and the physician's experience. Despite advanced diagnostic tests and increased clinical experience, there is no consensus on the definition of FUO, patient groups and diagnostic algorithm. Therefore, it is an issue that remains important worldwide and is open to research.

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