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ARAŞTIRMA / RESEARCH

Fever of unknown origin: evaluation of 30 pediatric patients

Nedeni bilinmeyen ateş: 30 çocuk hastanin değerlendirilmesi

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Abstract

Purpose: The aim of this retrospective study is to evaluate the etiology clinical and laboratory features of fever of unknown origin (FUO) diagnosed in 30 pediatric patients.

Materials and Methods: The clinical data including the etiology, diagnostic approaches and clinical characteristics were retrospectively analysed in 30 pediatric patients with FUO who presented to our clinic in oneyear period.

Results: The median age of the patients was 63 (6-192) months. Among the patients, 12 were male (40%), while 18 were female (60%). The median duration of the fever was 22.5 (3-60) days during hospital admission. The most common physical findings were hepatomegaly and splenomegaly, which were observed in 53. 3 and 40 patients, respectively. The cause of the FUO was detected to be infection in 14 patients (46.6%), connective tissue-vascular diseases in 8 patients (26.7%), malignancies in 5 patients (16.7%), and miscellaneous diseases in 1 patient (3.3%). In two patients (6.6%) the etiology could not be identified. Leishmaniasis, tuberculosis and Brucellosis were the most commonly identified infections, whereas juvenile rheumatoid arthritis and acute lymphoblastic leukemia were the most common non-infectious causes.

Conclusion: The most common cause of FUO in our study was infection diseases. Connective-vascular tissue diseases and malignancies are also important causes of FUO. In our opinion, detailed patient history, carefully physical examination and close clinical follow-up may reduce the number of the invasive procedures and non-invasive tests.

Keywords: Fever, fever of unknown origin, children, infection

Öz

Amaç: Bu çalışmada nedeni bilinmeyen ateş (NBA) tanısı almış 30 çocuk hastada etyolojinin, hastaların klinik ve laboratuvar özelliklerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Kliniğimizde bir yıllık süreçte NBA tanısı alan 30 çocuk hastanın ateş etyolojisini, tanısal yaklaşımlarını ve klinik özelliklerini içeren veriler geriye dönük olarak hasta dosyaları incelenerek elde edilmiştir.

Bulgular: Hastaların median yaşı 63 ay (6-192 ay) idi. Hastaların 12'si (%40) erkek, 18'i(%60) kız idi. Başvuruda ateşin süresi median 22.5 gün (3-60 gün) idi. Ensık saptanan fizik muayene bulgusu sırasıyla %53.3 ve %40 hepotomegali ve splenomegali idi. Nedeni bilinmeyen ateş nedeni olarak 14 (%46.6) hastada enfeksiyon, 8 (26.7) hastada kollajen vasküler hastalık, 5 (%16.7) hastada malign hastalık, 1 (%3.3) hastada diğer hastalık grubundan hastalık saptandı. İki (%6.6) hastada ateşin nedeni belirlenemedi. Nedeni bilinmeyen ateşin etyolojisinde Leishmania, tüberküloz ve brusellozis enfeksiyon hastalıklarından en sık tespit edilen neden iken juvenile romatoid artrit ve akut lenfoblastik lösemi enfeksiyon dışı ensık neden idi.

Sonuç: Çalışmamızda NBA'nın en sık nedeni enfeksiyon hastalıkları idi. Kollajen vasküler hastalıklar ve malign hastalıklar da NBA'nın önemli nedenlerindendir. Bize göre detaylı öykü dikkatli fizik muayene ve yakın klinik izlem uygulanacak invaziv işlemler ve invaziv olmayan test sayısını azaltacaktır.

Anahtar kelimeler: Ateş, nedeni bilinmeyen ateş, çocuk, enfeksiyon

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INTRODUCTION

Fever of unknown origin was first described in 1961 by Petersdorf and Beeson as fever persisting longer than 3 weeks, temperature higher than 38.3°C on several occasions and failure to reach a diagnosis despite 1 week of inpatient investigation[1]. In 1991, Durack and Street added the nosocomial, neutropenic and immune-deficient fever of unknown origin to the classic description[2]. Today, the third criterion has been modified as failure to reach a diagnosis despite 1 week of intensive investigation including abdominal tomography[3].

In pediatric patients, fever of unknown origin may develop due to various infectious and non-infectious causes. The underlying cause of fever of unknown origin is generally investigated in 5 categories as infectious diseases, malignant conditions, collagen vascular diseases, miscellaneous diseases and undiagnosed etiology. The frequency of these diseases varies according to the geographical region, age group and socio-economic conditions[4]. Infectious diseases and collagen vascular diseases are the most frequently revealed disease groups in the etiology of fever of unknown origin[5].

The aim of our study is the retrospective evaluation of the patients who were diagnosed with fever of unknown origin and followed up based on this diagnosis.

MATERIALS AND METHODS

For the purposes of this study, the patients who were diagnosed with fever of unknown origin at the Pediatric Infectious Diseases Clinic of the Çukurova University Medical Faculty between 2008 and 2009 years were retrospectively analysed. Fever of unknown origin was defined body temperature > 38.3ºC on several occasions and failure to reach a diagnosis despite 1 week of inpatient investigation[3]. 84 patients were excluded from the study. They were the patients who had been established with final diagnosis during hospital admission, patients who had known congenital or acquired immune deficiencies and patients who were diagnosed with malignancy.

After the detailed patient history of the patients who were diagnosed with fever of unknown origin in our clinic was recorded, they underwent a physical examination followed by the baseline tests including the complete blood count (White blood cell count, haematocrit level, thrombocyte level), peripheral smear, erythrocyte sedimentation rate and serum C-reactive protein level tests; serological assessments for Brucella, salmonella, Epstein-Barr virus (EBV), HIV, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, toxoplasmosis and Cytomegalovirus (CMV); urinalysis, urine culture, blood biochemistry (transaminase levels, serum urea nitrogen, serum creatinine, serum electrolytes, serum total protein and serum albumin level) blood culture, abdominal ultrasonography and chest X-ray. Patients in which no diagnosis could be made were applied further tests including the ANA, anti-DNA, tuberculin skin test, echocardiography, whole body scintigraphy, abdominal-thoracic tomography, bone marrow aspiration and biopsy, and pathological assessment or rapid antigen (RK-39) test for leishmania as required during the clinical follow-up.

According to the diagnoses made during the follow up, our patients were divided into five groups including infectious diseases (Brucellosis, cat scratch disease, leptospirosis, malaria, mycobacterial infections, salmonella infection, toxoplasmosis, tularemia, EBVinfection, CMV infection), collagen-vascular tissue diseases (Juvenile rheumatoid arthritis, systemic lupus erythematosus, polyarthritis nodosa), malignancies (leukemia, lymphoma), other diseases (drug fever, central fever), and undiagnosed conditions.

Statistical analysis

Statistical analysis was performed using SPSS software (Version 17.0, SPSS Inc., Chicago, IL, USA). Descriptive analysis (mean, standard deviation, freguencies) are evaluated and reported.

RESULTS

Thirty pediatric patients including 18 females (60%) and 12 males (40%) diagnosed with fever of unknown origin were included in our study. The demographic and clinical characteristics of the patients are presented in Table 1. The laboratory features of the patients are presented in Table 2. While 28 patients (93.3%) were diagnosed during the follow-up, no diagnosis could be made in 2 patients (6.7%). The diagnoses were classified in five groups as infectious diseases, collagen tissue diseases, malignancies, other diseases, and undiagnosed conditions.

Table 1. Clinical and demographic characteristics of the patients

Variables		
Age (months) Mean ±SD (Median) [Min-Max]	73.50 ±55.34 (63) [6-192]	
Sex, (n) (%)		
Male	12	40
Female	18	60
Duration of the fever Mean ±SD (Median) [Min-Max]	22.63 ±14.54 (22.50) [3-60]	
Additional complaints, (n) (%)		
Anorexia (most frequent complaint)	8	26.6
None	4	13.3
Physical examination (n) (%)		
Hepatomegaly	16	53.3
Splenomegaly	12	40
Hepatosplenomegaly	8	26.6
Rash	8	26.6
Lymphadenopathy	5	16.6
Normal Physical Examination	4	13.3

Table 2. Laboratory features of the patients

Variables	**Mean ±SD (Median) [Min-Max]**
White blood cells (WBC) mm^3	13480.1±2312.6 (11250) [683-47800]
Serum C-Reactive Protein (CRP) mg/l	116.458±13.860 (110) [5-224]
Sedimentation (mm/h)	77.62±6.418 (80)[16-140]
Hematocrit (%)	26.613±0.2 (27) [14.4-38.4]

The distribution of the patients according to the disease groups and the diagnoses are presented in Table 3. The most common diagnosis among the patients with fever of unknown origin was infectious diseases (46.6%); while visceral Leishmaniasis and tuberculosis were the most frequently diagnosed infectious diseases. The second most common diagnosis following infectious diseases was collagen tissue diseases with juvenile rheumatoid arthritis leading this group as the most frequently diagnosed disease. Among the five patients who were diagnosed with malignancies, four were diagnosed with leukemia while one patient had lymphoma. The fever in one patient was diagnosed as drug fever.

All our patients admitted due to fever of unknown origin underwent baseline examinations including complete blood count, peripheral smear, erythrocyte sedimentation rate and serum C-reactive protein level, urinalysis, urine culture, blood biochemistry, blood culture, abdominal ultrasonography, chest X-ray. Leishmania amostigote forms were detected in the bone marrow of the 6 patients who were diagnosed with visceral leishmania and the rapid antigen test for leishmania (RK39) was observed to be positive in these patients

Table 3. Diagnoses of the patients

Diagnoses	n	%
Infectious diseases	14	46.6
Visceral Leishmaniasis	6	20
Miliary tuberculosis	2	6.7
Pulmonary tuberculosis	2	6.7
Tuberculous lymphadenitis	1	3.3
Brucellosis	1	3.3
Salmonellosis	1	3.3
Liver abscess	1	3.3
Collagen tissue diseases	8	26.7
Juvenile rheumatoid arthritis	4	13.3
Unspecified collagen tissue disease	2	6.7
Systemic lupus erythematosus	1	3.3
Polyarteritis nodosa	1	3.3
Malignancies	5	16.7
Acute lymphoblastic leukemia	4	13.3
Lymphoma	1	3.3
Other diseases	1	3.3
Drug fever	1	3.3
Undiagnosed	2	6.7

Brucellosis was diagnosed by Positive Brucella agglutination test or positive blood culture. Salmonella infection was diagnosed by positive gaita or blood culture and Grubal-Vidal test in clinically compatible patient. Based on the chest X-ray, tomographic evaluation and pathological assessment, five patients were diagnosed with tuberculosis, among which one patient had tuberculous lymphadenitis, two patients had miliary tuberculosis and two other had pulmonary tuberculosis.

Juvenile rheumatoid arthritis (JRA) was the most frequently observed collagen tissue disease and 4 patients were diagnosed with JRA, while one had systemic lupus erythematosus and another was diagnosed with poliarteritis nodosa.

Two further patients were also diagnosed with collagen tissue diseases although the type of the disease remained unspecified. According to the bone marrow examination, 4 patients were diagnosed with acute lymphoblastic leukemia, while one patient had lymphoma. The lymph node biopsy in the patient diagnosed with lymphoma also supported the diagnosis.

Drug fever was considered in a patient who was

treated with phenobarbital against febrile convulsions and the fever returned to normal as the treatment was discontinued. No diagnosis could be reached in two out of the 30 patients (6.6%) evaluated during the study. The tests performed during the investigation of the underlying cause in the patients with a fever of unknown origin and the frequency of these tests are presented in Table 4.

Table 4. Diagnostic tests perfromed

Tests	n	%
Complete blood count	30	100
Peripheral smear	30	100
AST/ALT	30	100
Urinalysis	30	100
Chest X-ray	30	100
Ultrasonography	28	93.3
Salmonella serology	30	100
Brucella serology	30	100
Blood culture	30	100
Serological assessment	30	100
RK-39	20	66.7
ANA	20	66.7
Anti-DNA	20	66.7
Echocardiograghy	21	70
PPD	17	56.7
Rheumatoid factor	16	53.3
Immunoglobulin	26	86.7
Tomography	14	46.7
Scintigraphy	13	43.3
Bone marrow	24	80
Pathology	9	30

DISCUSSION

Fever of unknown origin continues to be a complicated problem since its diagnosis depends on geographical regions, socioeconomic conditions and the experience of the clinicians evaluating the patient. Another reason further complicating the diagnosis is the lack of a generally accepted diagnostic algorithm in spite of the developments in the diagnostic methods[3,4,6]. In developing and developed countries, the most common cause of the fever of unknown origin is infectious diseases. The underlying cause of the condition has been reported as infectious diseases in 10-78%, collagen vascular diseases in 2-22% and malignancies in 2-13% while 3-67% these patients could not be diagnosed in these studies[7-19].

Although changes have been made on the definition of fever of unknown origin with the development of new diagnostic methods, there is no consensus on its exact definition today. In the case series reported, the duration of the fever in unknown origin is considered to be varying from 5 days to 3 weeks. According to the differences in definition, the causes of fever with unknown origin are also different. In a study conducted by Cho CY et al., 126 patients were evaluated in Taiwan over a 10-year period. In this study, fever that lasted more than two weeks was considered as fever of unknown origin and the most common cause (27%) was infectious diseases. Ebstein-barr virus and CMV infection have been reported to be the most common infectious diseases. In this study, 16.6% of the patients were diagnosed with malignant diseases, 12.7% were diagnosed with autoimmune diseases and 23.8% of the patients could not be diagnosed[20]. In the study of Kim YS et al., where they evaluated 100 pediatric patients over a 15 year period, the cause of fever of unknown origin was defined as fever lasting more than 7 days. In this study, infectious diseases were 41.2%, autoimmune diseases were 27.5%, and malign diseases were 17.7%. 13.7% of the patients were diagnosed with other diseases or were not diagnosed[21].

In the present study, the etiology of FUO was revealed in 28 out of 30 patients (93.4%), while no etiologic cause could not determine in 2 patients (6.6%) The most frequent etiologic cause of FUO was infectious diseases (46.6%), followed by collagen vascular diseases with a frequency of 26.6%. Malignancies were observed in 16.7% of the patients. In two patients, in whom the cause of FUO could not be determined, the fever has resolved after within one mounth during follow up period.

The infectious causes of the fever of unknown origin include Brucellosis, tuberculosis and typhoid fever in developing countries; while osteomyelitis, tuberculosis and bartonellosis are more common in developed countries. The condition is more frequently associated with viral etiology in developed countries, with EBV infection leading the diagnoses. In a study conducted in our country, the most frequent infectious etiology of the fever of unknown origin was observed to be salmonellosis and Brucellosis[18,22]. In our study, Leishmaniasis and tuberculosis were the most common cause of fever of unknown origin, the latter being endemic in our country. Brucellosis and salmonellosis were observed to be the other infectious causes of the condition. One patient was diagnosed with chronic

granulomatous disease and the cause for the fever was found to be a liver abscess.

Visceral Leishmaniasis is a protozoal disease which is endemic in more than 80 countries and may cause high mortality rates unless treated. More than 90% of the cases has been reported from India, Bangladesh, Nepal, Sudan and Brazil. In our country, cases of visceral Leishmaniasis are closely related with the climatic conditions and are most frequently reported in the Mediterranean, Aegean and Central Anatolian regions[23,24]. Leishmaniasis, an infectious diseases commonly observed in our region, was also the most common infectious cause of fever of known origin, in our study. Juvenile rheumatoid arthritis is the leading one among the collagen vascular diseases that cause FUO[2,25,26]. Also in our study, juvenile rheumatoid arthritis was the most commonly diagnosed collagen vascular disorder.

Drug fever rarely causes fever of unknown origin in children, although it frequently leads to prolonged fever[3,27]. In our study, the fever was associated with Phenobarbital treatment in one patient and the patient's temperature returned to normal within 48 hours after the drug was discontinued. No fever was observed during the follow-up of this patient. In the literature, various algorithms have been proposed for the diagnosis of the fever of unknown origin[26,28,29]. However, subjecting each patient to these algorithms would lead to excessive testing.

In our study, subsequent to the recording of the detailed patient history and the physical examination, the baseline tests including complete blood count, peripheral smear, erythrocyte sedimentation rate and serum C-reactive protein level tests, serological tests, urinalysis, urine culture, blood biochemistry, blood culture, abdominal ultrasonography and chest X-ray were performed. Patients in which no diagnosis could be made were applied further tests including the ANA, anti-DNA, tuberculin skin test, echocardiography, whole body scintigraphy, abdominal-thoracic tomography, or rapid antigen (RK-39) test for leishmania as required during the clinical follow-up. Invasive procedures including bone marrow biopsies in 24 patients and tissue biopsies in 9 patients were performed.

In our opinion, a detailed patient history, carefully physical examination and close clinical follow-up may reduce the number of the invasive procedures and non-invasive tests, thus reducing the cost of the diagnostic procedures to be performed in these patients.

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