Fever of unknown origin in children: the experience of one center in Turkey

Hasan Tezer[1], Mehmet Ceyhan[2], Ateş Kara[2], Ali Bülent Cengiz[2], İlker Devrim[2], Gülten Seçmeer[2]

Departments of Pediatrics, [1]Gazi University Faculty of Medicine, and [2]Hacettepe University Faculty of Medicine, Ankara, Turkey. E-mail: hasantezer@yahoo.com

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Knowledge about the etiology of fever of unknown origin (FUO) has been changed under the influence of new advances in diagnostic techniques in both adulthood and childhood. Seventy-seven patients with the diagnosis of FUO were evaluated retrospectively. Forty-six (60%) of the patients were male and 31 (40%) were female, with ages ranging from 4 months to 16 years (mean: 4.5 years). Physical findings were absolutely normal in 33 (42.9%) patients, and the most common findings were hepatosplenomegaly (15.5%) and lymphadenopathy (15.5%). The etiologies were determined in 69 patients with FUO. The most common diagnoses were infectious diseases (50.7%), malignancy (14.4%), collagen vascular disorders (7.2%), and miscellaneous conditions (27.5%). With the development of diagnostic tools, the etiologies in a considerable number of patients with FUO were diagnosed. A detailed history and physical examination are required for accurate diagnosis, and if indicated, invasive procedures should be instituted.

Key words: fever of unknown origin, children.

Fever of unknown origin (FUO) is not commonly seen in childhood when compared to adulthood. In 1961, Petersdorf and Beeson (1) described for the first time FUO as fever lasting more than three weeks, with temperatures higher than 38.3°C as recorded several times, and which remained unidentified despite one week of evaluation in the hospital. Although this definition was the most frequently used, definitions of FUO remain controversial and variable[2-5]. In recent years, Durack and Street[6] suggested classification of FUO into four categories as classical, neutropenic, and nosocomial FUO, and FUO associated with human immunodeficiency virus (HIV). Durack and Street limited the duration of investigation to three days.

Although several detailed studies concerning the features, etiology and outcome of adults with FUO can be found in the literature[7-11], only a limited number of reports are available that include the etiology of children with FUO[12-18]. Not only the availability of new diagnostic techniques and radiographic methods, but also geographical features influence the distribution of etiologies in FUO.

In this study, we aimed to determine the etiology of FUO in children who were evaluated in a tertiary health care center located in central Turkey as well as the efficiency of classical and new diagnostic tools.

Material and Methods

In the present study, FUO was defined according to the classical Petersdorf and Beeson criteria as: fever >38.3°C on several occasions and persistent fever without diagnosis for at least three weeks despite investigation including hospitalization for at least one week. Patients with any previously known immunosuppressive disease (e.g. HIV positivity, leukemia, lymphoma) or suspected of having nosocomial infections were excluded from the study. Seventy-seven patients who were admitted to Hacettepe University, İhsan Doğramacı Children's Hospital between October 2005 and April 2007 with prolonged fever fulfilling the FUO criteria were

included in the study.

Medical reports of all patients were retrieved from a computerized database retrospectively, and all patients with FUO were evaluated prospectively. All patients had a detailed medical history and physical examination records. After this stage, the following laboratory investigations were performed step by step.

First phase: Complete blood count (CBC), erythrocyte sedimentation rate (ESR), peripheral blood smear, C-reactive protein (CRP), complete urine analysis, routine blood biochemistry, urine, stool and blood cultures, stool microscopy, and chest radiography were performed in all patients.

Second phase (due to results of tests in the first phase): Purified tuberculin test (PPD), nitroblue tetrazolium (NBT) test, anti-streptolysin O (ASO), antinuclear antibody (ANA), immunoglobulin (Ig) levels, complements 3 and 4, p-antinuclear antigens, serological tests for Epstein-Barr virus (EBV), mycoplasma, cytomegalovirus (CMV), toxoplasmosis, HIV, leishmaniasis, lyme, parvovirus, hepatitis A, B and C viruses, brucella, salmonella, and polymerase chain reactions (PCRs) for HIV and CMV were performed. Peripheral smears were also studied for malaria.

Third phase: Further radiological and invasive procedures including abdominal ultrasonography, computerized tomography (CT) scan , magnetic resonance imaging (MRI), bone marrow aspiration and biopsy, biopsy of lymph nodes, liver or other organs, molecular DNA analysis for familial Mediterranean fever (FMF) and hyper IgD syndrome, additional PCRs for Mycobacterium tuberculosis, echocardiography (ECHO), transesophageal echocardiography (TEE), and electromyelography (EMG) were performed if indicated. Lumbar puncture was performed upon suspicion of a central nervous system infection.

After evaluating children with prolonged fever according to the algorithms above, patients were categorized according to their etiology as fever due to infection, malignancy, collagen vascular disease, or miscellaneous conditions. If no evidence for the etiology of fever was detected and complete spontaneous recovery occurred, they were classified and defined as undiagnosed FUO.

Prior to enrollment in the study, an informed consent was obtained from the patient and his/her parents or local guardian and the study was approved by the Local Ethics Committee.

The statistical analysis was performed with Kruskal-Wallis variance analysis tests and chi-square tests by using the Statistical Package for the Social Sciences (SPSS) for Windows (SPSS Inc., Chicago, IL, USA).

Results

The mean age of the study group was 4.5±3.9 years old (range: 4 months - 16 years) and the median age was 3 years. Eleven children (14.3%) were under 1 year, 37 (48.1%) were 1-5 years, 24 (31.2%) were 6-12 years, and 5 (6.5%) were >12 years. Forty-six patients (59.7%) were male, while 31 patients (40.3%) were female.

The mean age was 4.9±4.0 (median: 3.0) years in patients with the infectious etiology, 2.3±1.8 (median: 2.0) years in patients with malignant diseases, 5.6±2.5 (median: 7.0) years in patients with collagen vascular diseases, and 3.6±5.3 (median: 1.1) years in patients with miscellaneous diseases. All the patients with collagen vascular diseases were aged 1-12 years while the patients in the malignancy group were less than 12 years old (Table I).

In 69 (89.6%) patients, the etiology was identified. Infections were found to be the most common cause of FUO (50.7%). The

Table I. Age Distribution of Patients with FUO

Causes (n)	<1 year (%)	1-5 years (%)	6-12 years (%)	>12 years (%)
Infection (35)	3 (8.6)	16 (45.7)	14 (40)	2 (5.7)
Neoplasm (10)	3 (8.1)	6 (16.2)	1 (2.7)	-
Collagen vascular disease (5)	-	2 (40)	3 (60)	-
Miscellaneous (19)	2 (10.5)	10 (52.6)	5 (26.3)	2 (10.5)
Undiagnosed (8)	3 (37.5)	3 (37.5)	1 (12.5)	1 (12.5)

other causes were as follows: malignancies in 10 (14.4%), collagen vascular diseases in 5 (7.2%), and miscellaneous diseases in 19 (27.5%) patients (Table II). The etiology of 8 (10.3%) patients remained unidentified despite investigation, and five of them showed spontaneous recovery.

The leading complaints of all patient groups were abdominal pain (25.8%), only fever (19.4%), myalgia and fatigue (15.5%), and arthralgia (11.5%). While the physical examination of 33 (42.9%) patients was normal, hepatosplenomegaly and lymphadenopathy were present in 31% of the patients, hepatomegaly in 6.4%, abdominal pain in 3.9%, membranous non-exudative tonsillitis in 3.9%, and muscular weakness in 3.9%.

Nearly 70% of the patients had a history of previous hospitalization, and 77.9% had a history of antimicrobial usage. Seventy percent of the patients had increased ESR (≥20 mm/hour) and 57.1% of the patients had elevated

Table II. Final Diagnosis

Cause	n	%
Infection	35	50.7
Enteric fever	5	
Urinary tract infection	5	
Epstein-Barr virus	4	
Respiratory tract infection	3	
Osteomyelitis	3	
Cytomegalovirus infection	3	
Brucellosis	2	
Tuberculosis	2	
Meningitis	1	
Dental abscess	1	
Parvovirus infection	1	
Kala-azar	1	
Giardiasis	1	
Human immunodeficiency virus	1	
Infective endocarditis	1	
Pott disease and psoas abscess	1	
Neoplasia	**10**	**14.4**
Acute lymphoblastic leukemia	4	
Acute myelogenous leukemia	2	
Juvenile myelomonocytic leukemia	1	
Myelodysplastic syndrome	1	
Langerhans cell histiocytosis	1	
Germ cell tumor	1	
Collagen vascular diseases	**5**	**7.2**
Juvenile rheumatoid arthritis	5	
Miscellaneous	**19**	**27.5**
Familial Mediterranean fever	8	
Kawasaki disease	3	
Diabetes insipidus	2	
Central fever	2	
Toxic polyneuropathy	1	
Hemophagocytic syndrome	1	
Chronic granulomatous disease	1	
Hyper IgD syndrome	1	
Total	**69**	**100**

Table III. Laboratory Parameters of the Patients

Groups	WBC min-max [mm³]	PLT min-max [mm³]	ESR min-max [mm/hr]	CRP min-max [mg/dl]
Infection	1500-22000 12531 ± 7157	26000-1137000 387514 ± 214561	5-88 34.3 ± 20.6	0.1-76 7.3 ± 13.1
Neoplasia	1400-97300 23350 ± 27863	7000-778000 325500 ± 247798	5-100 45 ± 32.1	0.1-10 4.2 ± 3.7
Collagen vascular diseases	11300-19200 15180 ± 3019	607000-800000 700800 ± 84307	87-105 87 ± 24.9	0.5-19.6 7.8 ± 7.1
Miscellaneous	5800-21000 11526 ± 5156	23000-659000 349684 ± 148498	2-69 28.9 ± 24.5	0.1-24 4.1 ± 6.4
Undiagnosed	2400-29500 29500 ± 12712	177000-899000 337712 ± 232268	2-46 17.7 ± 16.8	0.3-7 1.9 ± 2.3

CRP levels (≥1 mg/dl) (Table III). Nine percent of the patients had thrombocytopenia, 18% had thrombocytosis, 58.4% had anemia, and 26.4% had leukocytosis. The mean duration needed for the exact diagnosis of FUO was 8.2±5.9 (median: 6.0) days for infections, 11.4±6.8 (median: 10.5) days for malignancies, 6.4±2.8 (median: 6) days for collagen vascular diseases, and 17±10.4 (median: 18) days for miscellaneous groups.

Enteric fever and urinary tract infections were the most frequently observed infection in patients with FUO. Previous suboptimal antibiotic usage and negative blood and urine cultures were the main causes for delay in the diagnosis of enteric fever and urinary tract infections.

All patients with collagen vascular diseases had associated thrombocytosis and anemia, and 100% of these patients had elevated ESR and 80% had elevated CRP levels. There was no significant statistical difference between the other three groups according to means of white blood cell count, hemoglobin levels, and ESR ($p>0.05$). Platelet count and ESR were found to be significantly elevated in patients with collagen vascular diseases, when compared to the other three groups ($p<0.05$).

Non-invasive procedures were helpful in the diagnosis in 71% of the patients, while invasive procedures (cerebrospinal fluid (CSF) aspiration, bone marrow aspiration, lymph node

Table IV. Useful Diagnostic Procedures

Diagnostic procedure	n	%
Serology/PCR/Culture	21	30.4
Biopsy/aspiration	13	18.8
Clinical course	10	14.5
Radiology (CT/MRI/P-A thoracal graph)	9	13.0
DNA analysis	9	13.0
Water deprivation test	2	2.9
Bone scintigraphy	1	1.5
Transesophageal echocardiography	1	1.5
Lumbar puncture	1	1.5
Nitroblue tetrazolium test	1	1.5
Electromyelography	1	1.5
Total	**69**	**100**

biopsy, TEE) were useful in the diagnosis of 29% of the patients with FUO. Biopsy and bone marrow aspiration were observed to be helpful in visceral leishmaniasis, hemophagocytic syndrome, tuberculosis, and malignancies (Table IV).

Salmonella infections were diagnosed with a combination of Widal agglutination titers and isolation of *Salmonella typhi* in stool and blood cultures. The diagnosis of urinary tract infections was based on recurrent positive urine cultures. Among the infectious diseases, brucella diagnosis was difficult because of the negative blood cultures and non-specificity of brucella agglutination test. The diagnosis of respiratory tract infection was confirmed with chest radiography or thoracal CT. Two of our patients were diagnosed as central nervous system tuberculosis: one of them was diagnosed by cranial imaging methods/lumbar puncture (high protein, reduced glucose level and positive PCR) and the other by isolation of *Mycobacterium tuberculosis* in the CSF. EBV-specific antibody tests and blood CMV PCR and liver biopsy (in 2 cases) were useful for diagnosis of specific viral infections. In one patient, culture-negative endocarditis was diagnosed by TEE revealing vegetations and clinical findings. One patient with recurrent infections was diagnosed as HIV infection by HIV serology and Western blot method. CT revealed psoas abscess in one patient suffering vertebral deformity following a major trauma, and he was diagnosed as Pott disease. Another child with prolonged fever and rash was diagnosed as parvovirus infection with the positive parvovirus PCR and specific serological tests.

Among the malignancies, leukemias were the leading diseases, followed by myelodysplastic syndrome (MDS), cranial germ cell tumors, and Langerhans cells histiocytosis.

In our study, juvenile rheumatoid arthritis (JRA) was the only leading cause in the collagen vascular disease group that was diagnosed by excluding other diagnoses. Among the miscellaneous causes, the most common disease was FMF, which had varying atypical presentations that led to delay in diagnosis and required confirmation with DNA mutation analysis. For three patients with Kawasaki disease, the definite diagnosis was achieved with specific ECHO findings and clinical features. One patient with liver abscess was diagnosed as chronic granulomatous disease supported by NBT test. Other rare causes of FUO were toxic polyneuropathy, hyper IgD syndrome, secondary hemophagocytosis, diabetes insipidus, and central fever.

Three patients died during the study period. Two of the patients died from their primary disorders and one died before a diagnosis was obtained. The diagnoses of the two patients were HIV and solid malignancy.

Discussion

As new diagnostic techniques were developed, the conventional definition of FUO somehow lost its practical usage[4,8,19]. Since hospitalization for investigation for FUO increases expenditures, today, a trend of investigating patients with FUO as outpatients has been emerging, and FUO was redefined as fever that remains undiagnosed despite three or more outpatient visits[6]. While in some studies, FUO was defined as fever lasting for at least 14 days and uncertain diagnosis after the first investigation in the clinic[20,21], in our study, as in most of the studies in the literature, this duration was accepted as 21 days[18,22,23]. A careful medical history and physical examination are still the mainstays of the diagnostic approach in FUO[4,24-26].

The etiology of FUO in both adulthood and childhood has changed under the influence of new advances in diagnostic techniques. Thus, invasive procedures were required less often for the etiologic diagnosis in FUO. With the help of new diagnostic procedures, the ratio of undiagnosed cases with FUO has been decreasing in recent years[1,7,9]. Despite these advances, FUO remains an important and difficult problem for clinicians. The distribution of causative agents in FUO was reported to be affected by the child's age and the season in which the study was performed[7,9,12,15].

The most common etiological categories were reported to be infections, collagen tissue diseases and malignancies[15,17,18,20,27-30] in several studies from Turkey and other countries. Ordinarily, malignancies were reported to rank third following the collagen tissue diseases[15,18,20,27,28,31], but in our study, the ratio of malignancies in FUO patients (14.4%) was higher than the ratio of collagen tissue diseases

(7.2%). Since our hospital is a tertiary health care center and nearly all of our patients were referred from other hospitals, we assumed that collagen vascular disorders were more easily diagnosed with non-complicated tests compared to malignant diseases.

Infections were found to be the most common cause, reported by many studies as ranging from 32-86%[15,18,20,21,29-31]. In one study concerning FUO, while infections were reported to be present in one-third of the infants with FUO[20], its incidence declined for older ages. Pizzo et al.[15] reported that infections were found to be the cause of two-thirds of the prolonged fever in children under 6 years. Chiang and Chang[32] reported that the most common cause of prolonged fever in children was infectious disease, with the highest incidence according to age distributions in those under 2.5 years old. Respiratory tract infections were the most common form of infections in patients with FUO in these three studies. In our study, the leading cause of FUO in all age groups was infections, with the highest ratio (85.7%) in children between 1 and 12 years old. In our study, the infection ratio in young children was not as high as reported before[32]. This finding could be due to development of new molecular assays (real-time PCR, etc.), which were not available at the time of some of the other studies and have enabled a decrease in the ratio of undiagnosed respiratory infections.

Inappropriate usage of antimicrobial drugs, increased numbers of immunosuppressed patients, worldwide usage of antimicrobial drugs in poultry, and increased number of intensive care units had led to multidrug-resistant microorganisms that present themselves in a wide spectrum of diseases. Nearly 78% of our patients had a history of previous antimicrobial therapy before referral to our hospital. Previous antimicrobial usage prevents the isolation and growth of microorganisms in cultures and decreases the ratio of positive blood cultures (decreasing the amount of bacteria in circulation). Furthermore, previous antimicrobial therapy prevents the seroconversion in diseases such as enteric fever and salmonella infections. As a result, previous antimicrobial therapy is one of the factors playing a major role in the diagnostic delay in FUO patients. In five patients with previous antimicrobial usage history, the diagnosis of urinary tract infection was reached with multiple cultures after ceasing the antimicrobial therapy, confirming the negative effect of previous antimicrobial usage.

Primary CMV infections are rarely symptomatic in immunocompetent persons[33]. CMV causes a mononucleosis-like syndrome with clinical features such as prolonged fever, myalgia, and cervical lymphadenopathy[33]. EBV and early HIV infections should be differentiated in such cases[34]. Despite the advances in molecular biology, the diagnosis of viral diseases is not always easy for the clinician because of atypical presentations. In our cases, CMV infection was confirmed by specific serology and by using blood CMV PCR and in two patients with additional liver biopsy. Although all reported cases of CMV infections in immunocompetent patients have been self-limiting, there have been some sporadic cases, including our case, in which a deteriorated clinical condition was present and required specific antiviral therapy.

Since 20% of the patients with malignancies were reported to have osteoarticular findings[16], unsurprisingly, bone and joint pain/swelling are one of the key points in FUO patients for reaching a diagnosis. Since in these cases osteoarticular complaints were prominent, the diagnosis of malignancies could be reached with the help of bone marrow aspiration and biopsy[35,36]. In our study group, two of the 10 patients with malignancies had joint pain, and one patient had been misdiagnosed as collagen tissue diseases instead of malignancy. Another issue in our study was the patients whose bone marrow aspiration demonstrated blasts as less than 5% of the population, since this amount can be seen in chronic infections, drugs and metabolic disorders. One patient with FUO in our study was diagnosed as MDS after intense investigation with the help of bone marrow aspiration. Thus, in such cases, bone marrow biopsy could differentiate pediatric MDS from these diseases.

In conclusion, a final diagnosis was reached in 90% of the cases with FUO. Infections were the leading cause in all ages, followed by malignancies and collagen vascular disorders. Despite the advances in science and technology, FUO is still an important and difficult problem for clinicians. A careful and detailed medical

history and physical examination are required in addition to the new molecular investigation methods.

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