Journal of Microbiology, Immunology and Infection (2017) 50, 40–45

Available online at www.sciencedirect.com

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ORIGINAL ARTICLE

Clinical analysis of fever of unknown origin in children: A 10-year experience in a northern Taiwan medical center

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Received 12 April 2014; received in revised form 27 November 2014; accepted 19 January 2015
Available online 30 January 2015

KEYWORDS
Fever of unknown origin;
FUO;
Children;
Infectious disease;
Taiwan

Background: Fever of unknown origin (FUO) was first described in 1961 as fever >38.3°C for at least 3 weeks with no apparent source after 1 week of investigations in the hospital. Infectious disease comprises the majority of cases (40–60%). There is no related research on FUO in children in Taiwan. The aim of this study is to determine the etiologies of FUO in children in Taiwan and to evaluate the relationship between the diagnosis and patient's demography and laboratory data.
Methods: Children under 18 years old with fever >38.3°C for >2 weeks without apparent source after preliminary investigations at Taipei Veterans General Hospital during 2002–2012 were included. Fever duration, symptoms and signs, laboratory examinations, and final diagnosis were recorded. The distribution of etiologies and age, fever duration, laboratory examinations, and associated symptoms and signs were analyzed.
Results: A total of 126 children were enrolled; 60 were girls and 66 were boys. The mean age was 6.7 years old. Infection accounted for 27.0% of cases, followed by undiagnosed cases (23.8%), miscellaneous etiologies (19.8%), malignancies (16.6%), and autoimmune disorders (12.7%). Epstein-Barr virus (EBV) and cytomegalovirus (CMV) were the most commonly found pathogens for infectious disease, and Kawasaki disease (KD) was the top cause of miscellaneous diagnosis.

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http://dx.doi.org/10.1016/j.jmii.2015.01.001

Conclusions: Infectious disease remains the most common etiology. Careful history taking and physical examination are most crucial for making the diagnosis. Conservative treatment may be enough for most children with FUO, except for those suffering from malignancies.

Introduction

Fever of unknown origin (FUO) is defined as a well-documented fever with a body temperature >38.3°C (101°F) for at least 3 weeks without any apparent source after 1 week of investigation in a hospital.[1] It is generally accepted that a fever for >1 week in a child warrants further investigation, since most viral febrile episodes subside within 1 week. A fever that continues beyond 5—7 days, or one that occurs on and off, usually prompts parents to seek medical advice. For this reason, the inclusion criteria in recent systematic reviews on pediatric FUO are pediatric patients with a fever persisting for 1—2 weeks with negative preliminary investigations, or without a diagnosis after three outpatient visits.[2] These criteria are more acceptable to most primary care physicians.

The incidence of FUO ranges from 0.5% to 3% in all hospitalized children,[3] with the proportion of those diagnosed varying from study to study. Overall, an infectious illness is the most common cause of FUO in children (40—60%), followed by autoimmune disease (10—20%), malignancies (5—10%), and miscellaneous conditions (5—10%),[2,5] with 10—20% of cases being undiagnosed.[2,4] The number of undiagnosed cases is increasing, which may be due to improvements in diagnostic techniques so that illnesses which were previously thought to be among the causes are now diagnosed earlier before the onset of the FUO.[6]

The diagnosis of a prolonged fever in children requires extensive history taking, thorough physical examination, and a series of complementary laboratory examinations. A delay in ordering appropriate surveys and a failure to interpret the findings may lead to the actual underlying cause being missed, potentially resulting in a life-threatening condition. As there are currently no published studies describing the causes and distribution of FUO in children in Taiwan, the present study aimed to determine the etiologies of FUO among children in Taiwan, and compare the findings to previous research to elucidate the indicators of life-threatening conditions.

Materials and methods

This retrospective study analyzed the medical records of children aged <18 years old with a fever of >38.3°C for longer than 2 weeks without an apparent source after preliminary investigations at Taipei Veterans General Hospital from January 2000 to December 2012. The Institutional Review Board of Taipei Veterans General Hospital approved the study protocol (VGHIRB No. 2013-05-026B).

Children with a definitive diagnosis at the time of referral, any previously known congenital or acquired immunosuppressive deficiency, or malignancies were excluded. Data on age, sex, duration of fever, history of illness, physical examination findings, basic laboratory investigations such as white blood cell (WBC), differential, and platelet count, levels of hemoglobin, C-reactive protein (CRP), and ferritin, urinalysis, and urine and blood cultures were obtained. Further serum examinations including complement component 3 (C3), complement component 4 (C4), double-stranded deoxyribonucleic acid (dsDNA), antinuclear antibody (ANA), and virology studies were retrieved based on individual situations. Imaging studies such as chest X-ray, abdominal sonography, and computed tomography, and invasive procedures such as lumbar puncture and bone marrow aspiration were also recorded.

We made the diagnosis of cytomegalovirus (CMV), Epstein-Barr virus (EBV), and mycoplasma infection based on the clinical presentations using positive viral serologic tests; that is, positive CMV immunoglobulin (Ig) M antibody (Ab) and/or positive urine CMV culture, positive EBV-viral capsid antigen (EBV-VCA) IgM Ab with a four-fold increase of IgG titer in paired sera, and positive mycoplasma IgM Ab. Children presenting with injected tonsils, productive cough, and rhinorrhea were grouped into upper respiratory infection. The definition of central nervous system infection was based on clinical manifestations such as headache, neck stiffness, and fever, with cerebrospinal fluid (CSF) pleocytosis and low CSF sugar level. Urinary tract infection was diagnosed using positive urine cultures. Summer fever and central fever were diagnosed using clinical presentation and exclusion. Patients who had prolonged fever especially during midnight or early morning, along with some institutional symptoms such as anorexia, sleeplessness, and gastrointestinal illness, which resolved while staying in an air-conditioned room, were diagnosed as having summer fever. Central fever indicated the absence of a documented infection in the febrile patients with neurologic disease, such as brain tumor or traumatic injury. It resulted from the dysfunction of the regulatory center at the hypothalamus.

The definitive diagnosis, if any, and prognosis were documented according to the discharge notes and outpatient department records. After reviewing all of these data, the patients were categorized as having fever due to infectious disease, autoimmune disease, malignancy, or a miscellaneous condition. If the cause of fever was not identified, the case was classified as being undiagnosed.

Statistical analysis was performed using the Chi-square test (goodness-of-fit) with SPSS software (SPSS Inc., Chicago, IL, USA).

Results

One hundred and twenty-six children suffering from a prolonged fever of >14 days without an initial definite

diagnosis were enrolled. There were 60 (48%) girls and 66 (52%) boys, with a mean age of 6.7 years (range, 1 month to 18 years). Thirty-four (27%) children were aged 1 month to 2 years, 30 (24%) were aged 3—6 years, 17 (13%) were aged 7—10 years, and 45 (36%) were >10 years old.

Ninety-six cases had a definitive diagnosis, including 34 (27%) cases with infectious diseases, 25 (19.8%) with miscellaneous etiologies, 21 (16.6%) with malignancies, and 16 (12.7%) with autoimmune diseases (Table 1). Thirty (23.8%) cases remained undiagnosed.

Among the patients with infectious diseases, most (35%) suffered from upper respiratory infections. Six (17.6%) and five (14.7%) children with infectious diseases had systemic CMV and EBV infections, respectively. Five cases (14.7%) had urinary tract infections, with *Escherichia coli*, *Enterococcus species*, *Klebsiella species*, and *Pseudomonas aeruginosa* as the pathogens. The majority of patients with infectious diseases recovered after supportive management or antibiotic treatment and had relatively fair outcomes.

Twenty-five patients were diagnosed as having miscellaneous disorders, including 15 patients with Kawasaki disease (KD), two patients with central fever, one patient with summer fever, one patient with myelodysplastic syndrome, one patient with aplastic anemia, three patients with hemophagocytic lymphohistiocytosis (HLH), and two patients with histiocytosis.

KD accounted for more than half of the cases in this group (60%), with all of the patients being younger than 6 years old. Fourteen of them had received aspirin and intravenous Ig treatment. Those children with HLH and histiocytosis had relatively unfavorable outcomes compared to the other etiologies. Two of the three patients with HLH and one of the two patients with histiocytosis died despite intensive chemotherapy or bone marrow transplant. The patient with myelodysplastic syndrome also died after steroid pulse therapy and bone marrow transplant.

Of the 16 patients with autoimmune disorders, more than half (13 cases) had systemic lupus erythematous, all of whom were girls >10 years of age. Another two patients had juvenile rheumatoid arthritis, and the remaining patient had autoimmune cholangitis. After receiving methylprednisolone pulse therapy or immunomodulators, all of them were discharged under regular outpatient clinic follow up.

With regards to the children with malignancies, 18 patients had acute lymphoid leukemia (ALL) and three patients had lymphoma. Most patients smoothly completed a series of chemotherapy and were under regular outpatient follow up. However, two patients with ALL and two patients with lymphoma died due to sepsis while receiving chemotherapy.

The age distribution for the different etiologies is summarized in Table 1. In the autoimmune group, significantly

Table 1 Age distribution and final diagnosis of children with fever of unknown origin (FUO)

Diagnosis	*n*	%	1 mo—2 y (%)	3—6 y (%)	7—10 y (%)	>10 y (%)
Infectious disease	34	27	9 (7.1)	8 (6.4)	5 (4.0)	12 (9.5)
CMV infection	6	4.8	—	3	—	3
EBV infection	5	4.0	1	2	—	2
Mycoplasma infection	2	1.6	1	—	1	—
Upper respiratory infection	12	9.5	1	3	3	5
Urinary tract infection	5	4.0	4	—	1	—
CNS infection	3	2.3	2	—	—	1
Lymphadenitis	1	0.8				1
Autoimmune disease	16	12.7	—	—	2 (1.6)	14 (11.1)*
SLE	13	10.3	—	—	—	13
JRA	2	1.6	—	—	2	—
Autoimmune cholangitis	1	0.8	—	—	—	1
Malignancies	21	16.6	1 (0.8)	8 (6.3)	3 (2.4)	9 (7.1)
ALL	18	14.3	1	7	2	8
Lymphoma	3	2.3	—	1	1	1
Miscellaneous	25	19.8	17 (13.4)*	5 (4.0)	—	3 (2.4)
Kawasaki disease	15	11.9	13	2	—	—
Central fever	2	1.6	1	1	—	—
Summer fever	1	0.8	1	—	—	—
MDS	1	0.8	—	—	—	1
AA	1	0.8	—	1	—	—
HLH	3	2.3	—	1	—	2
Histiocytosis	2	1.6	2	—	—	—
Undiagnosed	30	23.8	6 (4.8)	9 (7.1)	9 (7.1)	6 (4.8)
Total	126	100	33 (26.2)	30 (23.8)	19 (15.0)	44 (35.0)

*$p < 0.01$.

AA = aplastic anemia; ALL = acute lymphoid leukemia; CMV = cytomegalovirus; CNS = central nervous system; EBV = Epstein—Barr virus; HLH = hemophagocytic lymphohistiocytosis; JRA = juvenile rheumatoid arthritis; MDS = myelodysplastic syndromes; *n* = number of patients having the specific diagnosis; SLE = systemic lupus erythematosus.

Table 2 The relationship between duration of fever and final diagnosis

Cause	14–30 d (%)	31–60 d (%)	>60 d (%)
Infectious disease	26 (20.63)*	7 (5.56)	1 (0.80)
Autoimmune disease	9 (7.14)	5 (3.97)	2 (1.59)
Malignancies	13 (10.32)**	6 (4.76)	2 (1.59)
Miscellaneous	20 (15.87)*	4 (3.17)	1 (0.80)
Undiagnosed	20 (15.87)*	8 (6.45)	2 (1.59)
Total	88 (69.84)	30 (23.81)	8 (6.35)

*$p < 0.01$, **$p = 0.005$.

more children were >10 years of age (87.5%) compared to the other age groups ($p < 0.01$). In this group, 76.9% suffered from systemic erythematous lupus. There were significantly more infants (68.0%) in the miscellaneous group ($p < 0.01$), 76.4% of whom were diagnosed with KD.

Regarding the relationship between duration and causes of FUO (Table 2), 88 patients (69.8%) had FUO within 30 days, and eight patients (6.35%) had FUO for >2 months. Twenty six of 34 (76.4%) patients in the infectious disease group, 13 of 21 (61.9%) patients with malignancies, 20 of 25 (80.0%) patients in the miscellaneous group, and 20 of 30 (66.6%) patients in the undiagnosed group had a fever within 30 days, which were significantly higher than in those with a fever for >60 days ($p < 0.001$, $p = 0.005$, $p < 0.001$, and $p < 0.001$, respectively).

In terms of the associated clinical findings (Table 3), the patients with infectious diseases tended to have poor appetite and activity. Symptoms of upper respiratory infections were also frequently found in this group. Body weight loss was more commonly seen among the patients suffering from autoimmune disorders, followed by those with malignancies. The patients in the miscellaneous group were associated with a higher frequency of skin rashes, whereas the patients with autoimmune diseases were characterized by arthralgia and myalgia. However, none of the above symptoms or signs showed a statistically significant relationship with the specific cause.

The correlations of laboratory data and etiologies are shown in Table 4. The WBC count ranged between $5 \times 10^9/mm^3$ and $20 \times 10^9/mm^3$ in most cases. A higher WBC count ($>20 \times 10^9/mm^3$) was found more frequently among the malignancy (23.8%) and miscellaneous (24.0%) groups ($p < 0.01$), which was mainly due to ALL and KD. The predominance of polymorphonuclear granulocyte was significantly more common (88%) in the miscellaneous group, autoimmune disease group (100%), and undiagnosed group (83.3%; $p < 0.01$). Elevated CRP levels (>1 mg/dL) were seen more commonly in the infectious disease and miscellaneous groups ($p < 0.01$). The hemoglobin level fell below 12 g/dL in the autoimmune disease, malignancy, and miscellaneous groups ($p < 0.01$). The platelet count was found to be significantly lower in the patients with autoimmune disorders (56.3%) and malignancies (80.9%), whereas the patients with KD tended to have thrombocytosis.

With regards to prognosis, nine of 126 cases (7.14%) died. Of these cases, two had ALL, two had lymphoma, two had HLH, one had myelodysplastic syndrome, one had histiocytosis with bone marrow involvement, and one had CMV infection. None of the patients who remained undiagnosed had unfavorable outcomes in this study.

Table 3 The association of clinical findings with causes of fever of unknown origin (FUO)

Associated clinical findings	Infections disease ($n = 34$)	Autoimmune disease ($n = 16$)	Malignancies ($n = 21$)	Miscellaneous ($n = 25$)	Undiagnosed ($n = 30$)
Poor appetite and activity	11 (32.4%)	6 (37.5%)	4 (19.0%)	4 (6.0%)	4 (13.3%)
URI symptoms/signs	15 (44.1%)	3 (18.8%)	6 (28.6%)	14 (56.0%)	8 (26.7%)
BW loss	3 (8.8%)	4 (25.0%)	3 (14.3%)	0 (0%)	2 (6.7%)
Lymphadenopathy	6 (17.6%)	2 (12.5%)	5 (23.8%)	5 (20.0%)	3 (10.0%)
Arthralgia/myalgia	3 (8.8%)	10 (62.5%)	7 (33.3%)	2 (8.0%)	1 (3.3%)
Skin rash	7 (20.6%)	5 (31.3%)	0 (0%)	14 (56.0%)	2 (6.7%)

BW = body weight; n = number of patients having the specific diagnosis; URI = upper respiratory infection.

Table 4 Distribution of laboratory data among each cause of fever of unknown origin (FUO)

Causes of FUO	WBC ($\times 10^9/mm^3$) (%)				Differential count		CRP (mg/dL)	Hb (g/dL)	PLT ($\times 10^3/mm^3$)	
	<5	5–10	10–20	>20	PMN	L	>1	<12	<150	>450
Infections disease	5 (14.7)	15 (44.1)	13 (38.2)	1 (3.0)	21 (61.8)	13 (38.2)	18 (53.0)*	22 (64.7)	—	4 (11.7)
Autoimmune disease	9 (56.2)	5 (31.2)	1 (6.3)	1 (6.3)	16 (100.0)*	—	6 (37.5)	14 (87.5)*	9 (56.3)*	1 (3.8)
Malignancies	10 (47.6)	5 (23.8)	1 (4.8)	5 (23.8)*	7 (33.3)	14 (66.7)	9 (42.8)	20 (95.2)*	17 (80.9)*	—
Miscellaneous	2 (8.0)	10 (40.0)	7 (28.0)	6 (24.0)*	22 (88.0)*	3 (12.0)	19 (76.0)*	24 (96.0)*	5 (20)	3 (12)
Undiagnosed	5 (16.7)	13 (43.3)	10 (33.3)	2 (6.7)	25 (83.3)*	5 (16.7)	12 (40)	17 (56.7)	4 (13)	5 (16.7)

*$p < 0.01$.
CRP = C-reactive protein; Hb = hemoglobin; L = lymphocyte predominant; PLT = platelet count; PMN = polymorphonuclear granulocyte predominant; WBC = white blood cell.

Discussion

The present study showed that FUO in children is still mainly caused by infectious diseases. Of these infectious diseases, upper respiratory infections were the leading cause, followed by systemic viral infections, with CMV and EBV as the most common pathogens. Previous reviews have also indicated similar results,[7,8] and previous studies have found that the incidence of infections decreases gradually as the patients get older.[9,10] However, there were no significant differences among the age groups in the present study.

In the miscellaneous group, KD was the cause of >50% of cases, a phenomenon rarely reported in previous studies. This may be the result of better diagnostic methodologies in the current study than in earlier studies, in which cases of KD may have been unrecognized. Furthermore, the annual incidence of KD in Taiwan is the third highest in the world (69/100,000 for children <5 years of age).[11] Therefore, when facing children younger than 5 years of age with a prolonged fever in Taiwan, KD should be kept in mind as one of the most likely diagnoses.

In the current study, three patients were diagnosed with HLH, two of whom died despite intensive chemotherapy and intravenous Ig treatment. The mortality rate was significantly higher than for other diseases ($p < 0.01$). A previous study reported that patients with HLH may not have a typical initial presentation, and that fever persisted for a median of 19 days before the diagnosis was made.[12] This may explain why a diagnosis is often delayed. Overall, the reported mortality rate of HLH is around 50%,[12,13] and prompt recognition of the disease is essential to allow for the initiation of appropriate therapy.

Malignancies have been reported in only a small percentage of cases of FUO in most studies (1.5—6%).[2,7—9,14] This is in contrast to adults with FUO, in which the incidence of neoplasms can reach up to 7—16%.[15,16] However, in our study, ALL and lymphoma accounted for 16% of cases, which is similar to previous adult studies. Most of our patients with ALL and lymphoma underwent scheduled chemotherapy without complications.

With respect to the correlation between fever duration and etiology (Table 2), approximately 70% of the patients had a fever within 30 days, with infectious disease as the leading cause, and only 6.3% had a fever lasting >60 days.

Although in our study there was no significant correlation between clinical presentation and etiology, many studies have stressed the importance of careful survey of symptoms/signs as significant factors in determining further management.[5,17]

Aside from clinical presentation, laboratory data may provide essential clues for a differential diagnosis. Elevated WBC and CRP are regarded as indicators for infection or inflammation.[18] Our results demonstrated a higher WBC count and CRP level among those with infectious diseases, and a predominance of polymorphonuclear granulocytes and a lower hemoglobin level in those with autoimmune disorders and malignancies. Furthermore, a high WBC count ($>20 \times 10^9/mm^3$) was noted in the patients with malignancies and KD. Platelet count was also addressed in our study because it is regarded as an acute phase reactant, and it was found to be significantly lower in the patients with autoimmune disorders and malignancies. In other words, thrombocytopenia may raise the awareness of the illness in these categories.

In addition to serum examinations, imaging can be helpful for diagnosis. Chest X-ray is usually the only radiological survey included in the initial work-up.[19] Computed tomography is also a helpful diagnostic tool in children with localized diseases, however, it has a relatively lower yield.[20] Positron emission tomography with F-fluorodeoxyglucose plays a role in the distinction between scarring or fibrosis and active tumors.[21—23] In the current study, none of the patients achieved a final diagnosis via nuclear medicine imaging or positron emission tomography studies, which is similar to previous studies.[24]

For prognosis, in previous studies patients have been observed clinically for progression of illness if there were no positive findings.[25] More than 80% of reported cases have not had a serious illness after a median follow up of 3.5 years.[26—28]

There are some potential limitations to our study. First, the definition of FUO varies widely in duration from study to study. Second, the database was retrieved from only one tertiary medical center with more complicated cases, and the incidence of severe infections, malignancies, and undiagnosed cases may be higher in this hospital setting. Consequently, the results may not be able to illustrate the current epidemiology of FUO in Taiwan. In addition, some of the enrolled cases are lacking definite cultures or molecular laboratory data. In addition, diseases such as KD have not been identified in earlier studies, and the prevalence of KD varies in different regions of the world. Newly-developed diagnostic technologies can also alter the distribution of etiologies.

In conclusion, a detailed history taking and careful physical examination are most crucial for children with FUO. Only when indicated by these investigations can laboratory data, imaging studies, or even invasive procedures augment the efficiency of making the diagnosis, especially when considering cost-effectiveness. Prognosis is determined primarily by the underlying disease, and to a lesser extent, by prompt diagnosis. The outcome is the worst for patients with neoplasms.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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