Fever of unknown origin: a retrospective study of 95 children in an Iranian referral hospital

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ABSTRACT

Fever of unknown origin (FUO) is a common manifestation in paediatrics and is a diagnostic problem especially in primary care. The present study aims to revue the causes of FUO in an Iranian referral tertiary care hospital. Information on 95 patients referred to the Children's Medical Center Hospital, Tehran, between 2004 and 2006 with a primary diagnosis of FUO was evaluated retrospectively. Infectious diseases were diagnosed in 26.3% (n=25) of the cases, while malignant and non-infectious inflammatory diseases constituted 7.4% (n=7) and 14.7% (n=14), respectively. Urinary tract infections, acute lymphoid leukaemia and Kawasaki disease were the most commonly diagnosed conditions. Urinary tract infection accounted for approximately half of the infectious cases (n=14). Conclusive diagnostic factors included history and examination in 21 cases, analysis of different specimens (i.e., urine analysis, urine culture, serology, peripheral blood and cerebrospinal fluid [CSF] examination) in 12 cases, culture in nine cases and serological tests in four cases. Infection and malignancy in patients aged under three years, and inflammatory diseases in patients aged over three years were more common. In patients aged under three years urine culture, bone marrow aspiration and peripheral blood smear proved more helpful in arriving at a final diagnosis of FUO, while in patients aged over three years, history and physical examination also contributed to the final diagnosis.

KEY WORDS: Child.
Diagnosis.
Fever of unknown origin.

Introduction

Fever is a common manifestation in various diseases, and infants and small children may exhibit fever as the only sign of underlying disease.[1] Although rising temperature is often brief, self-limiting and requires no extensive study and special treatment, some episodes of fever remain unexplained.

Fever of unknown origin (FUO) is a diagnostic problem, especially for physicians in primary care. The difficulties involved in taking a history from infants and small children sometimes result in clinicians resorting to invasive diagnostic methods.[2] An episode of FUO is characterised by body temperature higher than 101°F (38.3°C) that lasts at least 14 days, during which, despite complete physical examination, laboratory evaluation and screening, no clear cause for it can be found.[3]

Given the high prevalence of FUO and the importance of a proper diagnostic approach to achieve early diagnosis and proper treatment, different causes of FUO are of special importance. After history and physical examination, diagnostic tests may be needed, and the present study aims to identify common causes of FUO in an Iranian referral tertiary care hospital.

Materials and methods

Records were reviewed of 95 children aged under 15 years who fulfilled the criteria for FUO between 2004 and 2006 at the Children's Medical Center, Tehran, Iran. Fever of unknown origin was defined as a temperature ≥38.3°C (101°F) lasting more than three weeks with a diagnosis that remained uncertain after one week of hospital diagnostic work.[3]

Detailed information about the patients included in the study was collected, including their clinical characteristics (e.g., gender, age, fever feature, period of hospitalisation). In addition, results of microbiology, serology (e.g., for cytomegalovirus [CMV] and Epstein–Barr virus [EBV]), immunology (e.g., antinuclear antibody [ANA] and systemic lupus erythematosus [SLE]), imaging studies (e.g., chest X-ray [CXR]), history and physical examination were collected.

The cause of FUO was determined at the time of discharge or during follow-up. The causes were classified into four groups: infectious disease, malignant disease, non-infectious inflammatory disease, and undiagnosed. Data were analysed using SPSS-16 and the χ^2 test, and $P<0.05$ was considered to indicate statistical significance.

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Results

In the study population, 53 (55.8%) patients were male and 42 (44.2%) were female. Infectious disease was diagnosed in 26.3% (n=25) of cases, while malignant and non-infectious inflammatory disease constituted 7.4% (n=7) and 14.7%

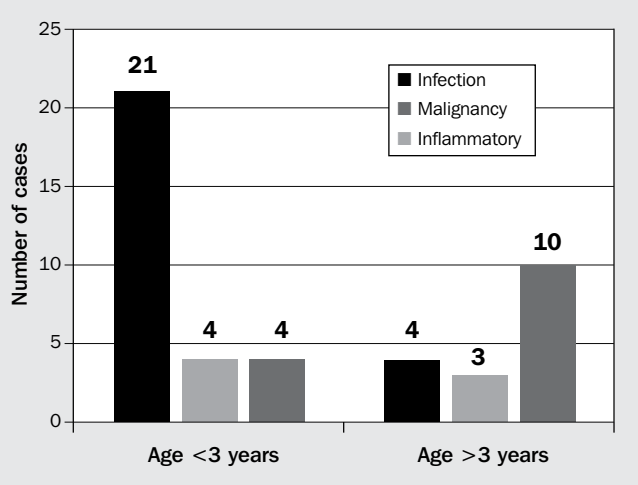

Fig.1. Prevalence of diagnosed diseases in two age groups (<3 year and >3 year) in children with a primary diagnosis of FUO.

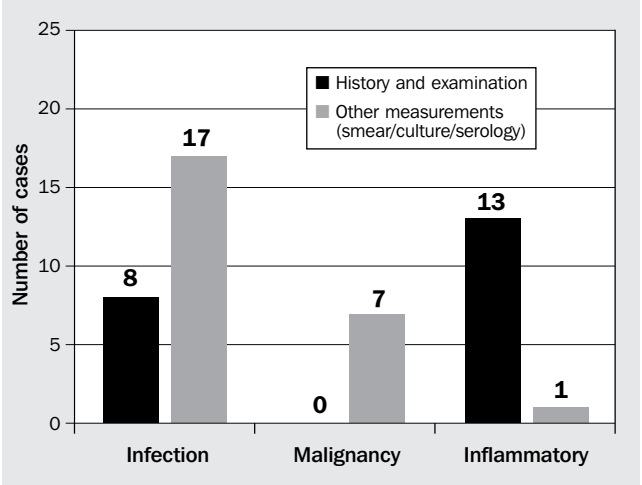

Fig. 2. Conclusive diagnostic test categories in children aged under 15 years with a primary diagnosis of FUO, 2004–2006.

(n=14), respectively. As can be seen in Table 1, urinary tract infection, acute lymphoid leukaemia and Kawasaki disease were the most common diagnoses. In the infection group, urinary tract infection (UTI) accounted for approximately half of the cases (n=14) attributable to infection. The most predominant microorganisms found in UTI were Gram-negative pathogens such as *Escherichia coli*, *Enterobacter* and *Klebsiella* species.

Serological tests were performed in 61 cases and positive findings were seen in eight, but it was conclusive in only four cases (viral serology for CMV and EBV, ANA in one case [SLE] and parasite serology in another [Kala-azar]). Analysis of blood, urine, biopsy and CSF, for example, resulted in positive findings seen in 38 cases and these were conclusive in 12. Culture was performed in 86 cases and positive findings were seen in 29 but the results were conclusive in only nine. Endoscopy did not lead to diagnosis in any of the cases. Imaging was undertaken in 84 cases and was positive

Table 1. Final diagnosis and conclusive tests used for diagnosis in children aged under 15 years with a primary diagnosis of FUO, 2004–2006

Category (n)	Diagnosis (number)		n	Conclusive test
Infection (25)	Viral (9)	CMV	1	Serology
		EBV	1	Serology
		Measles	1	History
		Viral infection	4	Physical examination
		Viral pneumonia	2	History + CXR
	Bacterial (15)	*Borellia*	1	PBS
		Colangitis	1	History + laboratory tests
		Pseudomonas sepsis	1	Blood culture
		Meningitis	2	CSF smear
		Pyelonephritis	1	Urine analysis
		Pharyngitis	1	Pharyngeal discharge, culture
		UTI	8	UA + UC
	Parasite (1)	Kala-azar	1	Serology
Malignancy (7)	ALL		4	PBS/BMA
	AML		1	BMA
	Hodgkin's lymphoma		1	Lymph node biopsy
	Non-Hodgkin's lymphoma		1	Lymph node biopsy
Non-infectious inflammatory (14)	JRA		5	Physical examination
	Kawasaki		7	Physical examination
	SLE		1	Physical examination + serology
	FMF		1	Physical examination
Unknown	–		49	–

CXR: chest X-ray, CSF: cerebrospinal fluid, UA: urine analysis, UC: urine culture, PBS: peripheral blood sample, ALL: acute lymphoblastic leukaemia, AML: acute myeloid leukaemia, BMA: bone marrow aspiration, JRA: juvenile rheumatoid arthritis, SLE: systemic lupus erythematosus, FMF: familial Mediterranean fever.

in 31 cases, but none proved conclusive. Full results can be found in Tables 1 and 2.

There was a significant relationship between age group and final diagnosis ($P=0.05$). Infection and malignancy were more common in patients aged less than three, while non-infectious inflammatory disease was more common in patients aged over three years (Fig. 1).

Discussion

The results of this study show that FUO was caused by infection in over a quarter of cases, followed by inflammatory disease and malignancy, and confirms previous finding.[4–15] Chien *et al*.[16] showed that bacterial and vial infections occurred in 19 and 17 cases, respectively, while the prevalence of SLE and juvenile rheumatoid arthritis (JRA) was similar to that found in the present study.

Overall, the most effective diagnostic procedures in the present study were history and physical examination, urine culture and bone marrow aspiration (Fig. 2). In work by Ciftci E *et al*..[17] biopsy, aspiration, serology, bacteriology, radiology and observation of the clinical course were shown to be the most useful diagnostic procedures, while in that by Chantada *et al*.,[18] history and physical examination led to a final diagnosis in 81% of case.

Failure to take a complete history, repeated physical examination and excessive and improper use of laboratory tests and imaging techniques are common errors in the diagnostic approach to FUO. After physical examination and history taking, the most useful diagnostic measures in the present study were urine culture and bone marrow biopsy.

Pizzo *et al*.[19] showed that children aged under six were more likely to have an infectious cause for FUO, while 80% of inflammatory disease occurred in the group older than six years. In the present study, infection was the top cause of FUO, with UTI the most common in this subgroup. In patients older than three years, due to the greater prevalence of non-infectious inflammatory disease, history and physical examination proved most useful, while in those under three, due to the higher prevalence of infection and malignancy, bone marrow aspiration and peripheral blood culture were more useful. □

Table 2. Conclusive diagnostic measurement categories in children aged under 15 years admitted to the Children's Medical Center with a primary diagnosis of FUO, 2004–2006.

Measurement			*n*	%
Physical examination and history			21	45.6
Culture	Urine	7	9	19.6
	Blood	1		
	Pharyngeal discharge	1		
Histological technique and specimen analysis	BMA	4	12	26.1
	CSF	2		
	Lymph node biopsy	2		
	PBS	2		
	Urine	2		
Serology			4	8

PBS: peripheral blood sample, BMA: bone marrow aspiration, CSF: cerebrospinal fluid

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