

Children with fever of unknown origin in Argentina: an analysis of 113 cases

GUILLERMO CHANTADA, MD, SANDRA CASAK, MD, JOSÉ DAZA PLATA, MD, JUAN POCIECHA, MD AND ROSA BOLOGNA, MD

The aim of this study was to determine the causes of fever of unknown origin, to evaluate new diagnostic tests and to elucidate risk factors for chronic or life-threatening disorders. The medical records of 113 children who had undiagnosed fever for at least 3 weeks were reviewed. Infection ($N = 41$) was the most frequent cause of fever of unknown origin. Respiratory tract infections were the most common causes in infants and endocarditis and tuberculosis were more frequent in older children. Neoplastic disorders ($N = 11$) occurred in children older than one year. Juvenile rheumatoid arthritis ($N = 9$) was the most common collagen-vascular disorder ($N = 15$). Miscellaneous disorders and factitious fever occurred in 21 and 4 cases, respectively. Twenty-two patients remained undiagnosed. History and physical examination led to a final diagnosis in 81% of cases. Abdominal ultrasonography was performed in 71 patients (61%) and was helpful for diagnosis in 15%. Children with life-threatening or chronic disorders ($N = 58$) were older than those with self-limiting conditions ($N = 55$; $P = 0.017$). Cardiovascular and articular signs and symptoms were more frequent in the former group ($P = 0.01$).

INTRODUCTION

The diagnostic evaluation of children with fever of unknown origin (FUO) in developing nations has not been studied thoroughly in recent years. In more developed countries it has been suggested that the advent of newer imaging studies and laboratory tests might have changed the previous picture.¹ Infections such as sinusitis, osteomyelitis and pyelonephritis are now less frequent causes of FUO. Instead some dis-

orders, such as cat-scratch disease, Kawasaki disease, Epstein-Barr virus infection or human immunodeficiency virus infection, may play a more significant role.¹

In order to describe the diagnostic spectrum of children with FUO and to elucidate factors that could provide the pediatrician information in addressing appropriate diagnostic tests and procedures, we undertook a study of 113 consecutive patients in a large tertiary care center in Argentina.

METHODS

Case definition. FUO was defined according to revised Petersdorf criteria² (a minimum temperature of 38.3°C and fever for 3 weeks after at least one week of intensive investigation). Patients with a previously detected immunodeficient condition were excluded.

For the purpose of this study a potentially life-threatening disorder was defined as a condition with a more than 10% case fatality rate with standard therapy and a chronic disorder was defined as any condition lasting for more than 6 months. These patients were included in Group I comprising malignancy, collagen-vascular disorders, infectious endocarditis, human immunodeficiency virus infection and central fever. Also four patients with factitious fever³ for more than six months and two patients who remained without specific diagnosis for more than six months were included in this group. Those patients who did not meet the above criteria were included in Group II.

Case ascertainment. Cases were identified by reviewing the medical records of all patients with FUO between November, 1987, and October, 1991. In order to avoid a possible bias in the selection of cases, the charts of all children with FUO as reported in other series were also reviewed.

Setting. Hospital de Pediatría Prof. Dr. J. P. Garrahan is a tertiary care pediatric center which serves Buenos Aires and surrounding areas (population about 11 000 000 inhabitants). An average of 2000 children are admitted each month and 20 000 are seen as ambulatory patients in the same period. Most patients

Accepted for publication Jan. 7, 1994.

From the Hospital de Pediatría "Prof. J. P. Garrahan," Buenos Aires, Argentina.

Key words: Fever of unknown origin, Argentinian children.

Address for reprints: Guillermo L. Chantada, M.D., J. Newbery 2562-Iro. "C," (1426) Buenos Aires, Argentina.

come from low income families and around 60% lack health insurance.

Statistical analysis. Data were stored and analyzed by EPIINFO version 5 (WHO 1989) software. The Mann-Whitney *U* test was used to compare age, gender, white blood cell count, duration of fever, hemoglobin and erythrocyte sedimentation rate.

Comparison of physical findings between Group I and Group II was achieved with Yates-corrected chi square analysis. Results were considered significant if $P < 0.05$ and they are expressed as mean \pm SD unless otherwise specified.

RESULTS

Patient population. A total of 113 patients fulfilled the criteria for FUO. Median age was 64 months (range, 3 to 234 months). Fifty-five percent were male. The median duration of fever when patients were first seen at our institution was 30 days and at least one course of antimicrobial therapy had been prescribed in 80% of cases. Final diagnoses are listed in Table 1.

Causes of FUO. Infections were the most common cause of FUO at all ages but their nature differed among the age groups. Respiratory tract infections (RTI) were the leading cause in infants ($N = 4$) and they were also common in children from one to five years old ($N = 2$). The clinical spectrum included patients with upper RTI (otitis media, $N = 4$; sinusitis, $N = 1$) and patients with lower RTI (lobar pneumonia, $N = 2$; and *Mycoplasma pneumoniae*, $N = 1$). Diagnosis was microbiologically or radiologically confirmed in all cases. Otitis media was confirmed by tympanocentesis. Fever subsided with therapy in all patients. All patients with abdominal abscesses ($N = 7$) had vague abdominal discomfort and two had hepatomegaly.

Liver enzymes were normal. In two additional patients abdominal ultrasonography showed regions of low attenuation in the liver, probably related to cat-scratch disease. One of them was confirmed by biopsy.

Three of six patients with tuberculosis had a positive tuberculin test. All cases of pulmonary tuberculosis presented with nonspecific respiratory symptoms and diagnosis was achieved by detecting a household contact.

All but one patient with infective endocarditis ($N = 7$), were older than five years and only two had a previously detected congenital heart anomaly. No congenital heart disease was subsequently found in the remaining patients. A pathologic murmur was audible in all cases, as were valvular vegetations detected by heart ultrasound. Blood cultures yielded a microorganism in five of seven patients with infective endocarditis.

Ten percent of our patients had a malignant disorder. All cases occurred in children older than one year. Acute leukemia and lymphoma accounted for one-half of the cases.

Juvenile rheumatoid arthritis was the most common collagen-vascular disorder that caused FUO ($N = 9$). Systemic lupus erythematosus was diagnosed only among the oldest children and all were girls. Miscellaneous disorders accounted for a substantial number of cases in our study. Kawasaki disease occurred in three children with a median age of 13 months. Suggestive skin lesions were observed in all cases. Two children had an incomplete form of Kawasaki disease, but all developed ultrasound proven coronary aneurysms. The mean duration of fever before hospitalization was 18 days.

Central fever occurred in three patients with central

TABLE 1. Final diagnoses in 113 children with fever of unknown origin according to age

0-11 months ($N = 21$)	12-59 months ($N = 40$)	60 or more months ($N = 52$)
Infection ($N = 9$; 43%)	Infection ($N = 11$; 28%)	Infection ($N = 21$, 40%)
Respiratory tract infection 4	Abdominal abscess 3	Infectious endocarditis 6
Urinary tract infection 1	Tuberculosis 2	Abdominal abscess 4
HIV infection 1	Respiratory tract infection 2	Soft tissue abscess 1
Infectious endocarditis 1	Meningitis 1	Tuberculosis 3
Tuberculosis 1	Epstein-Barr virus infection 1	Epstein-Barr virus infection 2
Epstein-Barr virus infection 1	Toxoplasmosis 1	Respiratory tract infection 2
Collagen-vascular diseases ($N = 1$; 5%)	Cat-scratch disease 1	Cat-scratch disease 2
Juvenile rheumatoid arthritis	Collagen-vascular diseases ($N = 5$; 13%)	Toxoplasmosis 1
Miscellaneous ($N = 7$, 33%)	Juvenile rheumatoid arthritis 4	Collagen-vascular diseases ($N = 9$; 17%)
Hemophagocytic syndrome 2	Undefined vasculitis 1	Juvenile rheumatoid arthritis 4
Central fever 2	Neoplasia ($N = 6$; 15%)	Systemic lupus erythematosus 3
Kawasaki disease 2	Neuroblastoma 2	Polimyositis 1
Nephrogenic diabetes insipidus 1	Acute nonlymphoblastic leukemia 1	Arthropathy, eye lesions and mental retardation 1
Undiagnosed ($N = 4$; 19%)	Hodgkin's disease	Neoplasia ($N = 5$; 10%)
	Myelodysplasia 1	Acute lymphoblastic leukemia 3
	Non-Hodgkin's lymphoma 1	Hodgkin's disease 1
	Miscellaneous ($N = 9$; 22%)	Myelodysplasia 1
	Hypogammaglobulinemia 2	Miscellaneous ($N = 4$; 8%)
	Kawasaki disease 1	Periodic fever 2
	Granulomatous hepatitis 1	Hemophagocytic syndrome 1
	Agranulocytosis 1	Acne fulminans 1
	Periodic fever 1	Factitious fever ($N = 4$; 8%)
	Reactive arthritis 1	Undiagnosed ($N = 9$; 17%)
	Undiagnosed ($N = 9$; 22%)	

nervous system malformations (hydrocephalus, $N = 1$; Arnold-Chiari malformation, $N = 1$; and corpus callosum agenesis with hypothalamic dysfunction, $N = 1$). Fever persisted for several months. Factitious fever occurred only in older children with a female predominance (F:M, 3:1). Severe family disorganization and personality disorders were found behind this poorly characterized sign. A history of other factitious illnesses was elicited in two patients. In an additional one Munchausen syndrome by proxy had been diagnosed elsewhere eight years earlier.

No cause of fever could be found in 22 children. All but two patients had a self-limiting disease and all have survived. These patients were significantly younger than the other 91 (mean age, 34 months; $P < 0.05$). Nine patients had a mononucleosis-like disease. Three patients had an upper RTI in which no viral cause was found by routine techniques; 19 patients underwent abdominal ultrasound with negative results in 14. In the remaining 5 patients nonspecific findings were detected but they did not contribute to final diagnosis.

History and repeated physical examination disclosed the final diagnosis in 84% of patients. An imaging study contributed to final diagnosis in 31% of cases. Abdominal ultrasonography was performed in 71 patients (61%) and it was suggestive or confirmatory of the final diagnosis in 15 cases (21%). Twenty patients (17%) underwent abdominal computed tomography scan which proved abnormal in 11 (55%). All these patients had an abnormal abdominal ultrasonography too.

Life-threatening vs. self-limiting disorders. Several differences in demographic, clinical and laboratory data were found between children with life-threatening or chronic diseases and those with self-limiting conditions (Table 2). Mean age was higher for children with life-threatening or chronic diseases than for those with self-limiting conditions (87 ± 62 months vs. 59 ± 55 months; $P = 0.02$). Also cardiovascular and joint signs were more frequent in the former, indicating poor prognosis.

DISCUSSION

The distribution of the diagnostic categories in our study was not substantially different from that in most series^{5,6}; however, some important characteristics were found. Our study included a large number of children with infectious diseases. This finding reflects the high frequency of these conditions in developing countries like Argentina even though endemic diseases were virtually absent in our series, probably because most patients came from urban areas. In fact it is probable that only the most difficult cases are referred to tertiary care centers⁷; therefore many children with FUO caused by common infectious agents are likely to be managed in primary care facilities.

TABLE 2. Demographic, laboratory and clinical differences between patients with chronic or life-threatening disorders (Group I) and self-limiting conditions (Group II)

	Group I ($N = 58$)	Group II ($N = 55$)	<i>P</i>
Patient data			
Age (months)	$87 \pm 62^*$	59 ± 56	0.02
Mean fever duration (days)	47 ± 45	42 ± 40	NS
Sex ratio (M:F)	1	1.5	NS
Laboratory data			
WBC (cells/mm ³)	$11\ 323 \pm 8298$	$12\ 190 \pm 5910$	NS
Hb (g/dl)	9.81 ± 2.2	9.7 ± 2.5	NS
ESR (mm/h)	61 ± 68	64 ± 38	NS
Physical findings			
Joint signs	25 (43)†	8 (15)	0.01
Cardiovascular signs	17 (28)	5 (9)	0.01
Hepatomegaly	11 (19)	12 (22)	NS
Splenomegaly	16 (28)	17 (31)	NS
Neurologic signs	12 (21)	4 (7)	NS
Skin lesions	18 (31)	19 (39)	NS
Weight loss	15 (26)	12 (22)	NS
Adenopathy	20 (34)	20 (37)	NS

* Mean \pm SD.

† Numbers in parentheses, percent.

WBC, white blood cell count; Hb, hemoglobin; ESR, erythrocyte sedimentation rate; NS, not significant.

Infective endocarditis was the leading cause of FUO in children older than five years. A high index of suspicion and the widespread use of blood cultures led to early diagnosis of infective endocarditis in adults in recent years.⁸ This is not the case in our setting because the index of suspicion for infective endocarditis by the general pediatrician is low, because it is often confused with rheumatic fever. In addition previous oral antimicrobial therapy in all our cases might have inhibited the growth of fastidious organisms causing a significant delay in diagnosis.

Tuberculosis is still an important cause of FUO in our series. Although it was relatively infrequent in most pediatric studies, recent data from adult patients suggest that tuberculosis is becoming more common as a cause of FUO in developed nations.⁷

Our study included a large number of children with abdominal abscesses. A recent series indicated that the number of adults with FUO caused by abdominal abscesses decreased because of the early use of abdominal ultrasonography.⁷ Abdominal abscesses are rarely considered in the differential diagnosis of children with FUO.⁸ Hence abdominal ultrasound should be performed early, especially if abdominal complaints are present.

The presence of some recently described disorders in our study, such as human immunodeficiency virus infection, Kawasaki disease and hemophagocytic syndrome, indicates that they should be considered in the differential diagnosis of children with FUO.¹

Despite the liberal use of newer diagnostic modalities, the number of undiagnosed cases of FUO has increased in recent years.^{7,10} The total number of patients remaining without a specific diagnosis may have been underestimated in our study because some

children with a self-limiting febrile illness are likely to have been missed, simply because only the difficult cases were referred to our center. Age distribution and clinical findings suggest that most of these children had an unidentified viral disease.⁵ Unfortunately adequate virology was not feasible in our study.

A major concern for the pediatrician evaluating a child with FUO is the rapid identification of conditions in which a diagnostic delay could be risky or even fatal. Our results suggest that older children were significantly at risk. In accordance with previous reports⁵ joint complaints often predicted serious diseases such as collagen-vascular disorders, infective endocarditis and leukemia. Cardiovascular findings were also significantly associated with poor outcome, probably because of the high frequency of infective endocarditis in our series.

In conclusion no simple approach can be outlined to evaluate children with FUO, but our list of crucial investigations includes a thorough history of disease, full physical examination of the patient and, to a rather limited extent, the use of laboratory and imaging techniques. Of these choices abdominal ultrasonography is one with a high benefit:cost ratio. This should be kept in mind in countries with limited resources.

ACKNOWLEDGMENTS

We are indebted to Pedro de Sarasqueta, M.D., and Ulises Questa, M.D., for their contribution to the preparation of the manuscript and to Heikki Peltola, M.D., for critical review of the manuscript.

REFERENCES

1. Pelton S. Fever of unknown origin. In: Stockman JA III, ed. *Difficult diagnosis in pediatrics*. Philadelphia: Saunders, 1990:175-82.
2. Petersdorf R. Fever of unknown origin: an old friend revisited. *Arch Intern Med* 1992;152:21-2.
3. Aduan RP, Fauci AS, Dale DC, Herzberg JH, Wolf SM. Factitious fever and self-induced infection: a report of 32 cases and review of the literature. *Ann Intern Med* 1979;90:230-2.
4. Port J, Leonidas JC. Granulomatous hepatitis in cat-scratch disease: ultrasound and CT observations. *Pediatr Radiol* 1991;21:598-9.
5. Pizzo PA, Lovejoy FH, Smith DH. Prolonged fever in children: review of 100 cases. *Pediatrics* 1975;55:468-73.
6. McClung MAJ. Prolonged fever of unknown origin in children. *Am J Dis Child* 1972;124:544-50.
7. Knockaert D, Vanneste L, Vanneste SB, Bobbaers HJ. Fever of unknown origin in the 1980s: an update of the diagnostic spectrum. *Arch Intern Med* 1992;152:51-5.
8. Larson E, Featherstone H, Petersdorf R. Fever of undetermined origin: diagnosis and follow up of 105 cases, 1970-1980. *Medicine* 1982;61:269-92.
9. Kaplan SL, Feigin RD. Pyogenic liver abscess in normal children with fever of unknown origin. *Pediatrics* 1976;58:614-6.
10. Steele RW, Jones SM, Lowe BA, Glasier CM. Usefulness of scanning procedures for diagnosis of fever of unknown origin in children. *J Pediatr* 1991;119:526-30.