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Clinical-epidemiological characterization of pediatric patients with fever of unknown origin

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Yunit del Pilar Foreman Linares I* https://orcid.org/0009-0003-5967-3656
Rolando Javier Alvarez Perez I https://orcid.org/0000-0003-0606-2993
YailínForeman Linares II https://orcid.org/0009-0004-4234-9259
IvanisIdael Corría MilánIII https://orcid.org/0000-0001-9934-2462
Mairelis Ortega Hernández I https://orcid.org/0000-0003-0524-7750

[I] University of Medical Sciences of Granma. Granma, Cuba.
[II] Provincial Clinical HospitalCelia Sánchez Manduley Surgical Hospital. Granma, Cuba.
[III] Jimmy Hirzel University Polyclinic. Granma. Cuba.

*Corresponding author: Email: foumanlinares1995@gmail.com

SUMMARY

Fever of unknown origin is one of the most common reasons for pediatric consultation and presents a diagnostic and therapeutic challenge for clinicians. To characterize pediatric patients with fever of unknown origin from a clinical and epidemiological perspective, a descriptive, observational, cross-sectional study was conducted on

pediatric patients with prolonged fever of unknown origin. The study population consisted of 62 patients discharged from the Hermanos Cordové Provincial Pediatric Teaching Hospital in Manzanillo, Granma, between January 1, 2022, and December 31, 2024. The predominant age range was over 11 years (45.1%). Fifty percent of the patients presented with prolonged fever, and 85.4% with the classic form. Fatigue was the predominant symptom in 77.4% of cases, and the most frequently used complementary test was the erythrocyte sedimentation rate (ESR) (93.6%). It was concluded that fever of unknown origin is more frequent in children over 11 years of age and that the classic form is present in more than a third of cases. Prolonged fever predominates. Fatigue and weight loss are the most frequently observed clinical manifestations. The most sensitive complementary tests are the erythrocyte sedimentation rate and the complete blood count, which may reveal varying degrees of anemia.

Keywords: Febrile illness; Fever of unknown origin; Indeterminate fever; Prolonged fever.

ABSTRACT

Fever of unknown origin is one of the most common causes of pediatric consultations and represents a diagnostic and therapeutic challenge for clinicians. In order to clinically and epidemiologically characterize pediatric patients with fever of unknown origin, a descriptive, observational, cross-sectional study was conducted in pediatric patients with prolonged fever of unknown origin. The population consisted of 62 patients discharged from the Provincial Pediatric Teaching Hospital “Hermanos Cordové” in Manzanillo, Granma, between January 1, 2022, and December 31, 2024. The predominant age group was over 11 years old, accounting for 45.1 %. Prolonged fever was present in 50 % of patients, and the classic form in 85.4 %. Fatigue was the predominant symptom in 77.4 % of cases. The most frequently used complementary test was the erythrocyte sedimentation rate (93.6 %). It was concluded that fever of unknown origin is more common in children older than 11 years and that the classic

form predominates in more than two-thirds of cases. Prolonged fever is the most frequent pattern. Fatigue and weight loss are the most commonly detected clinical manifestations. The most sensitive complementary tests are erythrocyte sedimentation rate and complete blood count, which often shows varying degrees of anemia.

Keywords: Febrile illness; Fever of unknown origin; Indeterminate fever; Prolonged fever.

SUMMARY

A fever of unknown origin is one of the most common causes of pediatric consultation and represents a diagnostic and therapeutic challenge for the clinician. With the objective of clinically and epidemiologically characterizing pediatric patients with fever of unknown origin, a descriptive, observational and cross-sectional study was carried out in pediatric patients with prolonged fever of unknown origin. The population was made up of 62 patients who were discharged from the “Hermanos Cordové” Provincial Pediatric-Teaching Hospital, in Manzanillo, Granma, during the period from January 1, 2022 to December 31, 2024. The predominant age group was those over 11 years of age, corresponding to 45.1%. Prolonged fever is present in 50% of two patients, the classic form in 85.4%. Fatigue was the predominant symptom in 77.4% of two cases. The most commonly used complementary test was the speed of hemosedimentação (93.6 %). It is concluded that fever of unknown origin is more frequent in children over 11 years old and that the classic form predominates in more than two thirds of cases. Predominant or prolonged febrile course. Fatigue and weight loss are only the most frequently detected clinical manifestations. The most sensitive complementary tests are the speed of hemosedimentation and the blood count, which frequently shows different degrees of anemia.

Key words: Feverish fever; Fever of unconflicted origin; Indeterminate fever; Prolonged fever.

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Introduction

Fever consists of an increase in temperature above the values considered normal. It is classified as low-grade fever or subfebrile state up to 37.9°C, moderate fever between 38°C and 39.9°C, and hyperpyrexia above 40°C. Nonspecific febrile syndrome is one of the most common reasons for pediatric consultation and poses a diagnostic and therapeutic challenge for clinicians due to the possibility of an underlying serious bacterial infection. (1,2)

The concept of fever of unknown origin (FUO) was first used in 1961 by Peterdorf and Beeson, who defined FUO as: fever greater than 38.3 °C at least twice a week; fever lasting more than 3 weeks; and fever whose etiological diagnosis remains undefined after 1 week of hospital study. (3)

In Cuba, this condition is more frequent in children under two years of age, with a temperature greater than 38 °C in 7 %. AA study conducted in Venezuela reports an incidence of 51% in males, with an average age of 18 months and a fever duration of one to two days in 70%. (4)

This syndrome has several etiologies, the most frequent being infectious, rheumatological, and hematological-oncological diseases, although in recent years this entity has been increasingly associated with patients carrying thehuman immunodeficiency virus (HIV), and Covid-19, already patients with secondary immunosuppression, which led to a classification of FUO into 4 categories: classic FUO, Petersdorf and Beeson criteria in immunocompetent non-hospitalized patients; FUO in HIV-infected patients; nosocomial FUO, and FUO in neutropenic patients (< 500 neutrophils/µl).[5]

The symptoms that accompany fever are varied and generally subjective. The most common clinical manifestations are chills, piloerection, sweating, increased heart and respiratory rate, myalgia, headache, warmth, cold sores, and nonspecific signs and symptoms such as asthenia, anorexia, and pallor of the skin and mucous membranes, followed by lymphadenopathy and headache. (6)

Although treatment is not a variable in this study, it is important to consider that broad-spectrum antibiotics can mask or delay diagnosis in some infections (bacterial endocarditis, central nervous system infections, osteomyelitis) because they produce negative microbiological cultures. However, this procedure should be considered in children at risk of severe bacterial disease and in those with significant clinical deterioration. Treatment of patients with fever of unknown origin (FUO) and good general condition should be symptomatic until the underlying etiology is clarified. (7,8)

Despite the multiple causes of fever of unknown origin (FUO) that occur in Cuba, especially in the current context, most cases go undiagnosed, often due to a lack of necessary resources and the absence of technological equipment in the health institutions where they are treated. (9)

Due to the difficulty of the diagnostic process of FUO, it is necessary for health personnel to know the characteristics of this disease, therefore the objective of this study is to clinically-epidemiologically characterize pediatric patients with fever of unknown origin.

Methods

A descriptive, observational cross-sectional study was conducted to characterize pediatric patients with prolonged fever of unknown origin. The study population consisted of 62 patients, treated at the Hermanos Cordové Provincial Pediatric Teaching Hospital in Manzanillo, Granma, during the period between January 1, 2022 and December 31, 2024.

Inclusion criteria:

- Patients diagnosed with fever of unknown origin.

- Patients under 18 years of age.

Exclusion criteria:

- Patients with incomplete medical records.

Variables studied:

Age:

>1 year, 1 to 3 years, 4 to 5 years, 6 to 10 years, 11 to 15 years.

FOD Course:

Prolonged, recurrent, and episodic.

FOD Classification:

Classic FOD, nosocomial FOD, FOD in neutropenic patient (< 500 neutrophils/µl).

Main signs and symptoms: fatigue, weight loss, lymphadenopathy, hepatomegaly, splenomegaly, joint pain, abdominal distension, heart murmurs.

Results of additional tests: Elevated erythrocyte sedimentation rate, anemia, leukocytosis, abnormal urinalysis, positive CRP, positive imaging studies (X-ray [Rx], computed tomography [CT]), and elevated transaminases. (Other complementary tests were not included as variables because they were not being performed at the institution during the study period.)

Information gathering:

The data obtained were entered into a database of the SPSS program version 22.0 for Windows, all the information was classified, protected and verified to be useful, the anonymity of each patient was respected and personal identity data was deleted.

Ethical aspects of research:

Existing ethical codes for research involving human subjects were respected, and informed consent was obtained from their parents or legal guardians (Appendix 1). The research was conducted with the approval of the Ethics Committee and Scientific Council of the Hermanos Cordové Provincial Pediatric Teaching Hospital. The ethical principles of autonomy, protection, beneficence, non-maleficence, and justice were also considered. Furthermore, the principles of the Declaration of Helsinki for the conduct of research involving human subjects were applied.

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Results

The predominant age range was over 11 years, in 28 patients (45.1%) (Table 1).

Table 1. Age distribution of children with prolonged fever of unknown origin (FUO).

Age (years)	No.	%
< 1	8	12.9
1 to 3	7	11.2
4 to 5	6	9.6
6 to 10	13	20.9
> 11	28	45.1
Total	62	100

Source: Medical Record.

When analyzing the clinical course of FUO, 31 patients (50.0%) adopted the form of prolonged fever with an average duration of 33.2 days, while 17 had episodic fevers (27.4%) (table 2).

Table 2. Prolonged course of FUO in studied children.

FOD Course	Average duration (days)	No.	%
Prolonged	33.2	31	50.0
Recurrent	51.3	14	22.5
Episodic	22.9	17	27.4
Total	35.8	62	100

Source: Medical Record.

According to the classification of fever, a total of 53 patients presented the classic form (85.4%), and in 6 there were significant neutropenias (9.6%) (Table 3).

Table 3. Classification of prolonged FUO in studied children.

FOD Course	No.	%
classic FOD	53	85.4
Nosocomial fever of unknown origin (FUO)	3	4.8
FOD in a neutropenic patient (< 500 neutrophils/µl).	6	9.6
Total	62	100

Source: Medical Record.

When analyzing the symptoms that occur in a case of prolonged FUO, fatigue was the predominant symptom in 48 cases (77.4%), the second most frequent symptom was weight loss in 38 cases (61.4%) (Table 4).

Table 4. Signs and symptoms in children with prolonged FUO.

Clinical manifestations	No.	%
Fatigue	48	77.4
Body weight loss	38	61.4
Lymphadenopathy	26	41.9
Hepatomegaly	16	25.8
Splenomegaly	14	22.5
Joint pain/arthritis	11	17.7
Abdominal distension	5	8.0
Heart murmurs	4	6.4

Source: Medical Record.

The most used complementary tests were the erythrocyte sedimentation rate in 58 cases (93.6 %), and the blood count with various degrees of anemia in 41 (66.1 %) (table 5).

Table 5. Results of complementary tests performed in children with prolonged FUO.

Results of the supplementary tests	No.	%
accelerated VSG	58	93.6
Various degrees of anemia	41	66.1
Leukocytosis greater than 11x109/L	29	46.7
altered cytology	25	40.3
Positive PCR test	24	38.7

Positive imaging studies (X-ray, CT scan)	12	19.3
Transaminases (ALT, AST) altered	11	17.7

Source: Medical Record.

Discussion

Fever of unknown origin (FUO) is a frequent reason for consultation in pediatrics. It can range from benign, self-limiting viral illnesses to bacterial infections, which present a diagnostic challenge. However, in most cases the cause is more or less evident after a thorough review of the medical history and the clinical course of the fever of unknown origin. (10)

A study by Bing Hu, et al., (11) reports that 41% of patients with FUO were in the age range of 6 to 12 years, results that differ from those obtained in the present study, this difference can be explained due to the social, demographic and epidemiological differences between the groups studied.

Ruiz Contreras, et al., (12) report that 50% of patients present with recurrent FUO, results that do not agree with those obtained in the present study, this may be due to the variety of etiologies of FUO, the way in which these behave, and the differences between the clinical pictures they cause.

Classic FUO occurs mostly in immunocompetent patients, without a history of prior hospitalizations that could explain nosocomial infections, and without apparent causes during the medical history and physical examination. Trapani S, et al., (13) in their research state that classic FUO is the most common presentation of this disease, results that coincide with those obtained in the present study. (8)

Maradiaga Montoya, et al., (14) identify anemia as the most frequent finding and report that 82% of patients with FUO suffered from it; however, the clinical condition that predominated in the patients of the present study was asthenia. This difference is due to the fact that anemia predominates in populations suffering from severe chronic,

infiltrative or neoplastic diseases, which are infrequent in the Cuban pediatric population.

It is important to analyze the symptoms that appear in a case of prolonged FUO, as they can be the harbinger of the underlying disease and guide an accurate diagnosis. Since FUO is a syndrome, it is necessary to characterize it from a clinical point of view, as the symptoms and signs will always depend on its origin; only fever and its accompanying symptoms constitute the most consistent manifestation. (15)

In the research carried out by WalaaShoman, et al., (16) the importance of laboratory tests as a fundamental piece for diagnosis is highlighted due to the specificity of these tests above others such as imaging, although these authors do not refer to a specific laboratory study these results agree with those obtained in the present study.

Conclusions

TheFever of unknown origin is most common in children between 11 and 15 years of age, and in more than a third of cases, it takes the classic form. Prolonged fever is predominant. Fatigue and weight loss are the most frequently observed clinical manifestations. The most sensitive diagnostic tests are the erythrocyte sedimentation rate and a complete blood count, which may reveal varying degrees of anemia.

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Conflict of interest

The authors declare that there is no conflict of interest.

Authorship contribution

Conceptualization and research: Yunit del Pilar Foreman Linares, Rolando Javier Álvarez Pérez, Ivanis Idael Corría Milán.

Data curation: Yunit del Pilar Foreman Linares, YailínForeman Linares, IvanisIdael Corría Milán.

Acquisition of funds: Yunit del Pilar Foreman Linares, Ivanis Idael Corría Milán.

Methodology, resources, supervision and validation: Yunit del Pilar Foreman Linares, Rolando Javier Álvarez Pérez.

Project Management: Yunit del Pilar Foreman Linares, Rolando Javier Álvarez Pérez, Yailín Foreman Linares.

Software: Yunit del Pilar Foreman Linares, Yailín Foreman Linares.

Visualization: Yunit del Pilar Foreman Linares, Yailín Foreman Linares, Rolando Javier Álvarez Pérez, Mairelis Ortega Hernández.

Original draft written by: Yunit del Pilar Foreman Linares, Yailín Foreman Linares, Mairelis Ortega Hernández.

Writing, review and editing: Yunit del Pilar Foreman Linares, Rolando Javier Álvarez Pérez, YailínForeman Linares, IvanisIdael Corría Milán, Mairelis Ortega Hernández.

ANNEX 1

Informed consent

Your child has been selected to participate in a clinical trial. Participation is voluntary, and you may withdraw from the study at any time without affecting the quality of your

medical care. Additional tests (blood, urine, imaging) and further clinical follow-up will be conducted to identify the cause of the fever. Potential risks are minimal and associated with routine procedures, such as discomfort from blood draws or exposure to imaging studies. Your personal and clinical information will be handled with strict confidentiality and used only for scientific purposes.

Rights:

Ask questions about the study at any time.

To decline to participate or withdraw from the study at any time.

Receive information about procedures, risks, and benefits.

I, _____, as the parent/guardian of _____, have read and understood the information provided. My questions have been answered, and I agree to my child's participation in the study.

___/_____/_____ _____

Date Signature