

PYREXIA OF UNKNOWN ORIGIN: AETIOLOGIC FREQUENCY IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: The aetiology of fever varies with age, sex, and geographical location. The most common causes fall in three main groups namely infections, collagen vascular diseases and malignancies. This study was conducted to know the frequency of different diseases causing pyrexia of unknown origin in patients admitted to a tertiary care hospital.

Material & Methods: This was a descriptive study of 100 patients with fever admitted to Medical Unit, Khyber Teaching Hospital Peshawar from March 2008 to March 2009. A detailed history and clinical examination was performed on admission and then periodically during the patient stay in the hospital. Based on the history and clinical examination, investigation plan was made. The preliminary laboratory investigations e.g. complete blood count, urinalysis, blood film examination and x-ray chest, were carried out. In every patient an attempt was made to isolate a causative micro-organism through cultures.

Results: Out of 100 patients 40 were males and 60 females. We were successful only in 83% of the cases to determine the cause. Majority (57%) had infective aetiology of which tuberculosis was at the top of the list (32%). The other diagnoses included neoplasms (10%), collagen vascular diseases (12%) and miscellaneous (3%).

Conclusion: Pyrexia of unknown origin is predominantly caused by infections led by tuberculosis and followed by typhoid fever, malaria and infective endocarditis. Collagen vascular diseases and neoplasms are next to infection. A significant number remains undiagnosed.

KEY WORDS: Pyrexia of unknown origin, Fever of unknown origin, Diagnosis, Causes.

INTRODUCTION

Pyrexial diseases are common worldwide and affect all age groups and both sexes.¹ Most febrile conditions are readily diagnosed on the basis of presenting symptoms and a problem focused physical examination.² Occasionally simple testing such as complete blood count or urine examination is required to make a definitive diagnosis. Viral illness e.g. upper respiratory tract infections account for most of the self limiting cases.³

In few cases, the aetiology is not established even after a detailed history, thorough clinical examination and routine investigations. Such prolonged febrile illnesses are termed as pyrexia of unknown origin (PUO) or fever of unknown origin (FUO).

The best definition of PUO was given by Petersdorf and Beeson⁴ in 1961 in a paper where they described 100 patients with PUO as "a temperature of 38.3°C (101°F) or greater on several occasions, more than 3 weeks duration of illness and failure to reach a diagnosis despite 1 week of inpatient investigations. While this definition has

stood for 30 years, recently it has been revised and the definition proposed by Durack and Street is based on a new classification of PUO. These are classical, nosocomial, neutropenic and human immune deficiency virus (HIV) associated FUO. Adaptation of these categories on a wide scale in the literature allows a more rational approach to the patients presenting with FUO.

The aetiology of PUO varies with age, sex, and geographical location. The most common causes fall in three main groups namely infections, collagen vascular diseases and malignancies.

The evaluation of a patient with PUO may prove to be a challenging task. History and physical examination may give clues for the working diagnostic plan.⁵

In recent years in the Western literature newly identified conditions like adult still's disease and neuroleptic malignant syndrome are increasingly reported to be responsible for PUO, so these conditions should be now added to the list of causes of PUO in our patients.

This study was designed to know about the current spectrum of diseases causing PUO in our set up.

MATERIAL AND METHODS

This descriptive study was carried out at Department of Medicine Khyber Teaching Hospital, Peshawar, for one year from March 2008 to March 2009. One hundred patients with prolonged fever fulfilling the PUO criteria of Petersdorf and Beeson were included in this study.

After taking informed consent, a detailed clinical history was obtained. All aspects of fever like its onset, character, duration, relieving and aggravating factors were recorded in detail on a specially designed proforma. A thorough review of systemic symptomatology was obtained. The musculoskeletal, skin, respiratory and abdominal symptoms were specially focused upon. The associated complaints of the ear, nose and throat were inquired. After systemic review, all aspects of relevant past, family, travel, occupational, surgical and sexual histories were obtained in detail. Finally a detailed history of current or past medications was also recorded in order to exclude the drug fever.

The history was followed by meticulous clinical examination on admission and on daily basis.

All except the most essential drugs were withdrawn. An accurate and hourly temperature chart in Celsius and Fahrenheit was recorded by the three trained and reliable staff nurses in their duty shifts. It helped us knowing the pattern of fever and also in excluding the possibility of factitious fever.

The clinical findings were discussed with other consultants who helped in planning a diagnostic workup.

The initial workup included the routine laboratory tests like complete blood counts, Erythrocyte sedimentation rate, x-ray chest, urinalysis, liver function tests, smears for malarial parasites, typhidot, urine and blood cultures. Some tests were repeated when found necessary. History and physical examination were repeated at each stage.

The decisions to obtain further diagnostic studies were based on abnormalities found in the initial tests. Imaging techniques like CT scans, MRI were carried out according to the continuous clinical assessment of the patients. More invasive procedures such as lumbar puncture, biopsy of bone marrow, liver, pleura, lymph nodes or aspiration of pleural, peritoneal or pericardial fluids were performed only when clinical suspicion showed that these tests were necessary.

All these and other relevant information were recorded in a objectively structured proforma. Studied variables were analyzed using SPSS version 11.

RESULTS

Out of 100 patients, 40 (40%) were males and 60 (60%) females. Age ranged from 15 to 71 with mean of 40 ± 6.32 years. Among female patients, 42 (70%) were younger than 30 years while in males most (90%) were older than 45 years. Majority 70% of patients belonged to rural areas. Twenty-five percent of patients were Afghan refugees.

Aetiology could be ascertained in 83 (83%) while 17 (17%) remained undiagnosed despite repeated clinical assessment and extensive diagnostic workup.

Out of 100 patients, 57 (57%) patients had PUO due to infections. Collagen vascular disease was responsible for 12 (12%) and neoplasm for 10% cases. Miscellaneous group comprised 4 (4%) cases.

Among the infections, 32 (32%) of total PUO cases, were due to tuberculosis. Most of the patients with tuberculosis were females i.e. 65%. Most of them were below 40 years of age. 22 cases were due to pulmonary TB while 10 due to extrapulmonary TB. Mycobacteria were cultured from different specimens in 20 cases. Ninety five percent of patients with tuberculosis were from rural areas.

The percentages of PUO due to malaria and typhoid fever were nearly the same i.e. 6% and 7% respectively. 50% of the malarial cases were due to plasmodium falciparum. Salmonella typhi was isolated in all the patients with typhoid fever either by blood (6 cases) or bone marrow cultures (1 case).

Table 1: Infections presenting as pyrexia of unknown origin.

Infections disease	Percentage
Tuberculosis	32
Typhoid fever	7
Malaria	6
Bacterial endocarditic	5
Brucellosis	4
Liver abscess	2
Ethmoidal sinusitis	1

Another common cause of infectious PUO was bacterial endocarditis. Five (5%) cases were documented. Four cases were found with history of previous cardiac lesions, mostly congenital heart diseases. Growth of different bacteria (mostly gram positive streptococci) was obtained through repeated blood cultures.

The second common aetiology was collagen vascular diseases responsible for 12 (12%) cases. Among these, 10 patients were females while 2 males. Most of the females were below 40 years of age. Among these 12 patients, systemic lupus erythematosus was found in 6 while Adult Still's disease and thyroiditis in 4 and 2 cases respectively.

Neoplasm was found in 10 (10%) cases. Out of these 10 cases, 8 (80%) were males while 2 (20%) females. Neoplasia caused PUO mostly in the younger patients i.e. 6 (60%) were younger than 30 years age. Non-Hodgkin lymphoma was at the top of the list i.e. 60%. Multiple myeloma caused 20% cases, acute myeloid leukemia (10%) and hepatoma (10%).

Among miscellaneous group (4%), sarcoidosis was found in 2, chronic pancreatitis in 1 and factitious pyrexia in 1 case.

DISCUSSION

The percentage of infectious diseases in our study was 57% which is comparable to the results of other studies like in Saltoglu et al (58%),⁶ Zamir et al (54.5%)⁷ and in Kejariwal et al (53%).⁸

Among infections, tuberculosis was the most common cause (32%). This percentage is much higher than the results of Saltoglu's study (17.2%).⁶ This is not unexpected as the disease is prevalent in Khyber Pakhtun Khwa province where more than 3 million Afghan refugees are residing in environmental conditions favourable to the transmission of tuberculosis. Fifty percent of the patients suffering from TB were Afghan refugees residing in the different villages of Peshawar. Majority of patients with PUO due to TB were females, i.e. 65%. This high percentage can be attributed to the gender discrimination in our society where due medical care to the female family members is not provided. So the diagnosis and proper treatment of female patients is often delayed. The prevalence of TB in younger age group i.e. less than 40 years in our study was noted. It shows the failure of TB control program and inadequate BCG vaccination.

The percentage of malaria in our study was found to be 6% while Iftikhar et al reported it to be 12.8%.⁹ The striking difference is due to the fact that clinical malarial cases (e.g. without confirma-

tory laboratory evidence but positive therapeutic response) were excluded from our study but included in the above mentioned study.

Plasmodium falciparum caused a significant number of PUOs i.e. 50%. It is due to the fact that plasmodium falciparum is rarely seen in the venous blood which is commonly taken for making blood smears. It lives in the capillaries of reticuloendothelial system. This is why capillary blood taken by finger prick or bone marrow smears diagnosed plasmodium falciparum malaria in our patients. Secondly chloroquine taken already by many patients before hospital admission could not cure their fever. It is chiefly because that plasmodium falciparum malaria is mostly resistant to chloroquine and partly because the dosage taken were improper.

The percentage of enteric fever in our study was 7%. This is lower than the Naseem's study of 11.8%.¹⁰ It could be because of many reasons the timing of collection of blood samples for culture might not have been appropriate for the stage of the disease process and the ideal time might have been missed. Some of our patients at the time of admission were already taking quinolones and other antibiotic which might have contributed to negative blood cultures. Thus the need for taking proper blood culture samples in all patients suffering from PUO is emphasized.

In our study blood and bone marrow cultures were positive for salmonella typhi in all the cases of enteric fever. It became possible only when the previous antibiotic therapy was stopped for 48 hours and then a proper blood culture (15 ml) taken. The cultures were found sensitive to quinolones and cephalosporins antibiotics.

In our study 12% of PUO cases were due to collagen vascular diseases. This finding is comparable to the studies from India by Kejariwal D et al⁸ (11%) and from Northern Pakistan by Iftikhar et al (13%)⁶. Among 12 patients with PUO due to collagen vascular diseases 10 were females. It is because of high prevalence of collagen vascular diseases among females.

The neoplastic diseases comprised 10% of the disease spectrum in our study. The percentage of neoplastic diseases presenting as PUO is different in different studies. A recent study by Zamir et al reported this percentage to be 7.9%⁷ while Iftikhar et al found that 19%⁶ of PUO cases were due to neoplastic diseases. Similarly Saltoglu et al reported 13.9%¹⁰ of prolonged fevers due to malignant diseases. However the number of neoplastic diseases presenting as PUO has decreased to less than 20%. It may be due to the availability

of more advanced and sophisticated imaging techniques which enable us to detect malignancies.

We have been successful in diagnosing 83% of cases but 17% remained undiagnosed. This finding can be compared to the study results of Khan et al from Mayo Hospital Lahore (22%).¹¹ The undiagnosed cases were advised regular checkup every fortnightly or to report if any new symptom or sign developed. Only 10 patients co-operated in follow up. All of them spontaneously improved except one patient who died 5 months later. Some of the undiagnosed patients did not come for follow up.

CONCLUSIONS

Pyrexia of unknown origin is predominantly caused by infections, lead by tuberculosis followed by typhoid fever, malaria and infective endocarditis. Collagen vascular diseases and neoplasms are next to infections. A significant number of PUO remains undiagnosed.

REFERENCES

1. Cherry DK, Woodwell DA. National ambulatory medical care survey: 2000 summary. *Adv Data* 2002; 328: 1-32.
2. Roth AR, Basello GM. Approach to the adult patient with fever of unknown origin. *Am Fam physician* 2003; 68: 2223-8.
3. Dykewicz MS. Rhinitis and sinusitis. *J Allergy Clin Immunol* 2003; 111 (suppl 2): 520-9.
4. Petersdorf RG, Beeson PB. Fever of unexplained Origin, report of 100 cases. *Medicine* 1961; 40: 1-30.
5. Kuperwasser LI, Darius H, Muller AM, Martin C, Mohr KS, Erbel R, et al. Diagnosis of culture

negative endocarditis: the role of the Duke criteria and the impact of transesophageal echocardiography. *Am Heart J* 2001; 142: 146-52.

6. Iftikhar AM, Shahid N, Suhail AB, Karomat AK, Aftab A, Muhammad 1, et al. Aetiology of pyrexia of unknown origin (PUO) in northern Pakistan. *Pak J Med Res* 1998; 37: 151-5.
7. Zamir D, Leiboviz I, Polychuck I, Reitblat T, Weiler Z, Zamir C. Fever of unknown origin in Israel. *Acta Clin Belg* 2003; 58: 356-9.
8. Kejariwal D, Sarkar N, Charaborti SK, Agarwal V, Roys J. Pyrexia of unknown origin: a prospective study of 100 cases. *Postgrad Med* 2001; 47: 104-7.
9. Naseen S, Ali K. Pyrexia of unknown Origin. The author's experience at Liaquat National Hospital. *Focus (fever)* 1997; 19.
10. Saltoglu N, Tasova Y, Midikli D, Aksu HS, Sanli A, Dundar IH. Fever of unknown origin in Turkey evaluation of 87 cases during a nine-year-period of study. *J Infect* 2004; 48: 81-5.
11. Khan APH. Study of etiological incidence of pyrexia of unknown origin in OPD Mayo Hospital Lahore. *Ann KE Med Coll* 1997; 3: 36-7.

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