Short Communication

Clinical profile of classical Fever of unknown origin (FUO)

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Abstract

Background: The etiology of fever of unknown origin (FUO) may differ from different countries. This study was conducted to evaluate the etiology of FUO in patients attending SKIMS, a tertiary care teaching hospital, at Srinagar, Kashmir, India.

Methods: From July 2010 to September 2012, this study was done to examine the profile of patients with FUO. The classic FUO was defined as three outpatient visits or three days in the hospital without elucidation of cause of fever. Infectious agents, collagen vascular diseases and hematological malignancies as well as other etiologies were investigated when appropriate. The data were collected and analyzed.

Results: A total of 91 cases (62 males and 29 females), with age ranging from 16 to 80 years were investigated. The mean duration of fever before hospitalization was 26±4 days. The etiology of FUO was delineated in (66%) of cases, whereas, (25%) remained undiagnosed. Most common group of FUO was that of infectious diseases (44%) followed by collagen vascular diseases and malignancies (12 % each). Amongst the infection group, brucellosis and salmonellosis comprised the majority of cases (25% each).

Conclusion: Infections are the most common cause of FUO followed by collagen vascular diseases in our region.

Keywords: Fever of unknown origin, Classical, Infectious diseases, Collagen vascular diseases.

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Fever is one of the common presenting symptom in clinical practice. Most of the time fever is either self-limiting or with a definite underlying etiology. If fever remains persistent and undiagnosed, it is termed as fever of unknown origin (FUO). Classically FUO was defined by Petersdorf and Beeson's (1) as a temperature above 38.3^0C (101^0F) on several occasions over a period of more than 3 weeks, for which no diagnosis has been reached despite 1 week of inpatient investigation. They observed that FUOs were caused by infection in 36% of cases, malignancy in 19%, and collagen vascular disease in 19% and miscellaneous causes in 19%. No cause was detected in 7% of cases. The percentage of undiagnosed "fever of unknown origin" had dropped from over 75 percent in the 1930s to less than 10 percent in the 1950s (2, 3). Since then, the fraction of FUOs that go undiagnosed has steadily increased, despite the introduction of various serological assays or improved imaging techniques.

Presently, the definition of FUO does not require one week in patient evaluation. Durack and Street divided FUO into four groups classical, nosocomial, HIV related and neutropenic (4). The etiology of FUO varies with geographical location. Various studies done previously reported that FUO is predominantly caused by infections, neoplasms and connective tissue diseases (5-9).

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The present study was undertaken to look at the etiologies of classical FUO in patients reporting to a tertiary care hospital in the north of India.

Methods

This present study on FUO was a prospective study that was carried out in the Department of Internal Medicine, SKIMS, Kashmir, India, a tertiary care hospital, for a period of two and a half years. The classic FUO is defined as three outpatient visits or three days in the hospital without elucidation of cause of fever. In our study, we wanted to search the etiology of such patients and to elucidate their clinical profiles.

The present study was undertaken from July 2010 and concluded in September 2012. A total of 91 cases were included in the study after proper consent and ethical clearance that fulfilled the criteria for classical fever of unknown origin (1).

A detailed history was taken from the patients, including the history of travel, risk of venereal diseases, hobbies, drug abuse, and contact with animals. After history, a detailed general physical and systemic examination was performed, which was repeated on daily basis to look for any evidence of underlying etiological cause of fever. Four hourly temperature charts were maintained to look for pattern of the fever.

Initial investigations included complete blood count with erythrocyte sedimentation rate, peripheral blood smear for malaria (if required), sputum examination especially for gram staining and AFB staining, chest x-ray, liver function tests, renal function tests, urine analysis, ultra-sonography of abdomen, urine and blood cultures. Further diagnostic tests performed including, serological tests for typhoid, brucella, viral hepatitis, tuberculin skin test, immunological markers like ANA/ RF, thyroid function test.

Imagings including contrast CT or MRI, echocardiographies were done if needed. They were based on the results of initial tests or clue from daily examination. More invasive investigation including lumbar puncture, pleural, pericardial or ascetic fluid analysis, lymph node aspiration or excision, bone marrow aspiration, biopsy and culture or liver biopsy were done if indicated by examination, lab or imaging tests. Statistical analysis of the data were carried out using Minitab (MTB 11). Chi- square test of significance was used to assess the correlation between pairs of categorical variables. A p-value < 0.05 was considered as significant. The study got approval from the Research and Ethics Committee of the Sheri Kashmir Institute of Medical sciences.

Results

A total of 91 cases of classical FUO was observed in two and a half-year period. There were 62 males (69%) and 29 females (21%), with age ranging from 16 to 80 years. Most of the patients (74%) were in the age group of 16-49 years. The mean duration of fever before hospitalization was 26±4 days, (table 1).

The most common findings on clinical examination were pallor, lymphadenopathy and splenomegaly. All the three findings were predominantly seen in patients with malignancy as a cause of FUO. The mean hemoglobin of patients varied from 7.71±3.2 mg/dl, total leukocyte court of 4.84±3.0 cells/mm^3, MCV from 76.95±3.3 and ESR from 21.66±2.8 mm. Hemoglobin tends to be on lower side in malignancy and connective tissue group (malignancy group 8.48±2.7, connective tissue group 7.71±3.2). Abnormality in liver function tests was observed in all groups with deranged kidney functions tests predominantly in collagen vascular disease group (chart 1).

Diagnosis of FUO was achieved in 77% (n=66) of cases, whereas, 27% of cases (n=25) remained undiagnosed. Out of 66 cases, diagnosis was possible, infections were the most common cause of FUO (44%), followed by malignancies (12%), and connective tissue disorder (12%).

Infections caused by bacteria dominated the group with (77%) followed by viral (12.5%) and protozoan infections (7.5%) (table 2). Brucellosis (25%), enteric fever (25%) and tuberculosis (17.5%) were the predominant bacterial infections seen in our series. Among the 7 patients of tuberculosis as a cause of FUO, 5 patients had disseminated tuberculosis and 2 had tubercular meningitis. Malaria was reported in 3 (7.5%) cases, and all patients had recent travel outside the valley. FUO caused by viruses was observed in 12.5 % of cases, caused by Episten Barr Virus in 4 (10%) cases and Cytomegalovirus in 1 (2.5%) case. Collagen vascular diseases were responsible for (12%) cases of FUO, predominantly affecting less than 40 year age group with maximum percentage (82%) constituted by females (n=9). Out of the 11 cases of connective tissue diseases, 9 had systemic lupus erythematous and 2 had adult Still's disease

(ASD). Neoplasm as a cause of FUO was seen in 12% of patients. Lymphoma constituted most of them (n=6). Among the miscellaneous causes,Kukuchi's disease was seen in two cases, 1 was diagnosed as hemophagocytic syndrome secondary to hepatitis B and 1 patient had hyperthyroidism as cause of his fever.Chart (2) relative frequency of disease is a category in FUO (table 3). In 25 (27%) cases, diagnosis was not possible; these patients were followed up till 6 months duration. All of them became afebrile except one patient who died within 3 weeks of admission. He was thoroughly investigated but basic etiology was undicernable. He scummed to secondary bacterial infection and septicemia.

Table 1: Sex and age of patients with FUO

Age group	Male %	Female %
16-40	53.33	21.11
41-60	14.28	6.5
>60	1.09	4.3

P<0.05

Table 2: Patients with infection as a cause of PUO (n=40, 43.96%)

Bacterial (n=31, 77.5%)		Viral (n=5, 12.5%)		Protozoal (n=4, 10%)	
Type	N (%)	Type	N (%)	Type	N (%)
Brucellosis	10 (32.26)	EBV	4 (80)	Malaria	4
Salmonellosis	10 (32.26)	CMV	1(20)	P.Falciparum	1(25)
Tuberculosis	7 (22.60)			P.Vivax	3(75)
Infective **endocarditis**	4 (12.90)				
Total	31 (100)		5 (100)		4(100)

Table 3: Other etiology FUO other than infectious agents

Inflammatory/Connective tissue disorder (n=11, 12.09%)		Malignant (n=11, 12.09%)		Miscellaneous (n=4, 4.39%)	
Type	N (%)	Type	N (%)	Type	N (%)
SLE	8 (72.7)	Lymphoma	6 (54.54)	Hyperthyroidism	1 (25)
Adult stills disease	2 (18.18)	Renal carcinoma	1 (9.09)	Hemophagocytosis	1(25)
Sarcoidosis	1 (9.09)	Colon cancer	1 (9.09)	Kikuchi's disease	2 (50)
		Leukemia	3 (27.27)		
Total	11 (100)		11 (100)		4 (100)

Discussion

In our series of 91 cases of classical FUO, that were observed over a period of two and a half years, the diagnosis of a specific cause was established in 66 cases (77%), with 25 cases (23%) remained undiagnosed.

We observed that in most of the cases of FUO were due to infectious diseases. Similar results were reported by various studies from Asia and the Middle East (10, 11). Infection still remains the most common cause of classical FUO all over the world even though the demographics vary from region to region (8). Infections were followed by connective tissue disorders (12%) and malignancies (12%) as a cause of FUO. Enteric fever, brucellosis followed by tuberculosis remained the most common infections observed in our series, contributing to FUO. Jung et al from India reported 233 cases of FUO and observed that enteric fever and tuberculosis constituted maximum percentage of FUO

(11). Although in India, approximately 80% of the population has close contact with domestic or wild animals owing to their residence or occupation, carrying a risk for zoonotic diseases including brucellosis, but only less than 10% of cases of FUO are attributed to brucellosis as evident from various studies from India (12). This could be explained by either the disease is overlooked or difficulty in correct diagnosis. Studies from the Middle the East (areas of maximum disease burden) by Al-zubaidy and Al-Fadhli reported almost similar percentage of FUO caused by brucellosis, as seen in our study (13, 14).

Tuberculosis still remains the important cause of FUO, especially the extra-pulmonary tuberculosis. Tuberculosis constituted 17.5% of infectious causes of FUO in our series, and none of the patients had pulmonary tuberculosis. Five cases had disseminated tuberculosis and two had tuberculosis meningitis. Kejariwal D et al from India observed his series of 100 cases of FUO, 53% were attributed to tuberculosis, predominantly extra pulmonary. Sharma et al. reported 50% cases of FUO caused by tuberculosis in northern India (5, 15).

Although malaria is rarely seen in our part of the world, we reported that 7.5% cases of FUO had malaria. All cases were caused by plasmodium falciparum, and none had complicated malaria. The history of recent travel outside the valley was present in all cases.

Diagnosis was made based on peripheral blood film and antigenic testing. Almost similar results were reported by Ishaq Khattak et al. from Pakistan (16). Viral cause of FUO detected in four cases was caused by Epstein-Barr virus and one by cytomegalovirus. Barbado et al. postulated that nowadays, infections, mainly of viral origin including cytomegalovirus or chronic Epstein-Barr virus infections are more prevalent (10). Because of lack of availability of virus isolation in our set up, most of the viral fevers remain undiagnosed.

The incidence of collagen vascular disease contributing to FUO in our series was 12%, it is consistent with the percentage reported by others (5, 14) Systemic lupus erythematous remained the most common collagen vascular disease found in our patients as it was reported by Barbado et al. (17). All cases happened to be females, because the incidence of CVD is higher in females. SLE was missed initially because of less common presenting symptom. Most of them had fever, lymphadenopathy and arthritis. Neoplastic diseases comprised of 12 % cases of FUO in our series. Various authors have reported malignancy between 10-20% as a cause of FUO. Kejariwal et al. and Ramamoorthy et al. estimated an incidence of 17% and 3.61% of malignancy as a case of FUO, respectively 14, 18). Lymphomas accounted to 6 cases (54.54%), 2 had (18.18%) of leukemia, 1 had (9.09%) renal cell carcinoma and one colorectal cancer (9.09%). Lymphomas comprised the most common cause among malignancy in our study which is consistent with a study done in Mexico with 75% incidence among malignancies (19).

In the present study, among the rare causes of Kikuchi's disease was found in two (2.91%) cases. One case had hemophagohistiocytosis related to hepatitis B virus. These cases are limited to case reports only. Wurn et al. reported a case of Kikuchi's disease as FUO and postulated that it is readily diagnosed on lymph node biopsy (20). Hyperthyroidism presenting primarily as persistent fever is extremely rare. A case of hyperthyroidism was diagnosed, which turned out to be Graves' Disease. Shaked et al (21). found a case of FUO who was suffering from hyperthyroidism. The incidence of FUO of indeterminate cause ranges from 4.7% to 19% (5, 22).

In our study, it was 27%, which may be attributed to a lack of more specialized tests used in FUO protocol, including PET scan etc.

In the present study, we believe the unavailability of better facilities like PET scan, various viral marker probes, immunofloresence and electron microscopy etc. would have marked a difference in establishing the cause of fever in undiagnosed patients.

Conclusion

The present study concludes that infections remain the main group of diseases in the evaluation of fever of unknown origin. The present study also gives an inference that malignancy and collagen vascular diseases also comprise the next big group of FUO.

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