FEVER OF UNKNOWN ORIGIN IN IMMUNODEFICIENT PATIENTS

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Introduction: Fever of unknown origin (FUO) is one of the major challenges for the physician. The aim of this work is to study FUO in two categories of immunodeficient patients: HIV infected and neutropenic patients.

Immunodeficiencies: There are two main classes of immunodeficiencies: primary immunodeficiencies, due to defects of lymphocytes, granulocytes and of the complement system, and secondary immunodeficiencies, such as the acquired immunodeficiency syndrome caused by HIV infection, immunodeficiency due to secondary neutropenia, cancers, transplants, corticosteroid therapy, diabetes and others. The immunodeficiency in HIV infection appears due to the decrease in number and impaired function of the CD4+ T helper lymphocytes, whereas in the case of neutropenia it is due to the decrease in the number of circulating neutrophils.

Fever of unknown origin: FUO is classified into four major categories: classical FUO, nosocomial FUO, neutropenic FUO and HIV associated FUO. Classical FUO is defined as fever above 38 degrees Celsius lasting for a period of at least 3 weeks, without a diagnosis during 3 outpatient visits or 3 days of hospital stay. It can be produced by infections, tumors, autoimmune inflammatory diseases, miscellaneous causes and it can remain undiagnosed in 10% of the cases. Nosocomial FUO is defined as fever above 38 degrees Celsius in inpatients, without the presence of incubation of disease at admission, without a diagnosis during 3 days of investigations. It can be produced by nosocomial infections, postoperative complications, drug fever, septic thrombophlebitis, pulmonary embolism, sinusitis, Clostridium difficile colitis. Neutropenic FUO is defined as fever above 38 degrees Celsius without a diagnosis during 3 days of investigations in the hospital, in patients whose neutrophil counts are below 500/mm³. It can be caused mainly by infections, such as opportunistic infections, Gram-negative bacterial infections, aspergillosis, candidaemia, herpesvirusues, and the cause remains unknown in 40-60% of the cases. HIV associated FUO is defined as fever above 38 degrees Celsius without diagnosis for more than 3-4 weeks in outpatients, and more than 3 days in inpatients, with confirmed HIV infection. It can be caused by acute HIV infection, mycobacterium tuberculosis and atypical mycobacteria, cytomegalovirus, lymphomas, toxoplasmosis, cryptococcosis, Pneumocystis carinii pneumonia, and other opportunistic diseases and tumors. The cause can also remain undisclosed in about 10% of the patients.

Material and method: A retrospective chart review was performed using the data of 59 HIV infected patients (admitted in the 1st Infectious Diseases Clinic of Tg. Mures, the National Institute of Infectious Diseases „Prof. Dr. Matei Balș” of Bucharest and „Szent László” Hospital of Budapest between 1998-2009), and 30 neutropenic patients (admitted in the 1st Haematology Clinic of Tg. Mures between 1999-2008) with FUO. Age, gender, stage of the HIV infection, T CD4+ and T CD8+ lymphocyte count, HIV viral load, the presence of antiretroviral and TMP-SMX therapy, the baseline disease in the neutropenic group, neutrophil and leucocyte count, duration of fever, duration of hospitalization, time until diagnosis was established, diagnostic tools, causes of FUO, treatment and outcome were noted and compared in the two groups of patients.

Results: Results in the group of patients with HIV and FUO: The mean age was 26.41±15.49 DS years, 69.49% were males, 82.14% were in stage C3 of the HIV infection, the mean T CD4+ lymphocyte count was 107.78±139.89 DS/mm³, the mean T CD8+ lymphocyte count was 587.45±446.92 DS/mm³. The mean viral load was 705147.25±798356 DS copies/ml, without any patient with undetectable viral load. 76.27% of patients were not receiving antiretroviral therapy at the beginning of FUO. 24.13% received TMP-SMX prophylaxis. The mean neutrophil count was 3870.94±3176.4 DS/mm³, the mean leucocyte count was 5022.34±3639.7 DS/mm³. The mean duration of fever was 61.89±61.81 DS days, the mean duration of hospitalization was 39.17±20.40 DS days, and the time until the establishment of diagnosis was 53.45±62.18 DS days.

The diagnostic methods that conducted to the cause of FUO were lymph node biopsy with histopathology (15.25%), pneumological examination (11.86%), serial chest x-rays, empirical therapy for tuberculosis (10.16% both), CSF examination, blood and urine culture, abdominal ultrasonography, empirical antiretroviral therapy, exclusion of other diseases (5.08% each), bronchoalveolar fluid examination, syphilis serology, abdominal CT scan, sputum samples for tuberculosis, oncological examination, empirical steroid therapy, empirical therapy for atypical mycobacteria (3.38% each), pleural fluid samples for tuberculosis, cytology of ascitic fluid samples, faeces samples for tuberculosis, cardiac ultrasonography, bacteriology of sputum samples, chest CT scan, liver and bone marrow histopathology, empirical cytostatic therapy, tumor markers and stop of the antiretroviral therapy (1.69% each).

FUO was caused by infections (59.37%), tumors (6.25%), miscellaneous causes (6.25%) and no diagnosis was obtained in 28.12% of the HIV infected patients. The main cause was mycobacterial infection (34.37%), including lymphonodular (10.93%), pulmonary (7.81%), pleural, pericardic, peritoneal and meningeal tuberculosis (1.56% each), disseminated and lymphonodular atypical mycobacteriosis (1.56% each), unspecified mycobacterial infection (6.25%). Other causes were pneumonias (6.24%), including Pneumocystis carinii pneumonia (3.12%), Aspergillus pneumonia and lung abscesses (1.56% each). Sepsis was another cause of FUO (4.68%), produced by Salmonella typhimurium, E. coli, Bacillus (1.56% each). Other infectious causes were HIV infection itself (4.68%), urinary tract infections (3.12%) caused by E. coli, Group D Streptococcus (1.56% each), syphilis (3.12%), cryptococcal meningitis (1.56%), Whipple disease (1.56%). The tumors that caused FUO were non Hodgkin lymphoma (4.68%) and liver...
cancer (1.56%). Miscellaneous causes of FUO were the immune reconstruction syndrome (3.12%), drug fever (1.56%) and wasting syndrome (1.56%). The outcome of FUO was favorable in most of the cases, with a death rate of 11.86% in the first month, 8.47% in the first 6 months, and repetition of FUO in 5.08% of the cases.

**Results in the group of neutropenic patients with FUO:** The mean age was 54.2±15.05 DS years, 50% of the patients were males. The baseline disease of the neutropenic patients with FUO was acute myeloid leukemia (48.48%), chronic lymphoid leukemia (12.12%), non-Hodgkin lymphoma (9.09%), acute lymphoid leukemia (9.09%), myelodysplastic syndrome (6.06%), myeloma multiplex, chronic myeloid leukemia, drug-induced agranulocytosis, pancytopenia in a patient with systemic vasculitis (3.03% each). The mean neutrophile count was 293.82±211.41DS/mm³, the mean leukocyte count was 1793.76±1964.2DS/mm³. The mean duration of fever was 16.24±16.83DS days, the mean duration of hospitalisation was 20.16±10.25DS days and the mean time until the establishment of diagnosis was 15.3±16.86DS days.

The diagnostic methods that conducted to the cause of FUO were blood culture (23.33%), chest x-rays (10%), pneumological examination (6.66%), bacteriology of sputum samples, chest CT scan, surgical examination, empirical antifungal therapy with Voriconazol (3.33% each). FUO had only infectious causes in the neutropenic patients, with 61.29% of the cases without diagnosis. The main cause of fever in the neutropenic group was sepsis (22.58%), caused by coagulase-negative staphylococci (16.12%), E. coli, Candida (3.22% each). FUO was caused by pneumonia in 16.12% of the cases (Staphylococcus aureus, Candida glabrata – 3.22% each -, Aspergyllus pneumonia – 9.67%). The outcome of the neutropenic patients with FUO was relatively favorable, with a death rate of 16.66% in the first month, 26.66% in the first 6 months, and the repetition of FUO in 10% of the cases.

**Comparative results in the two groups of patients:** The mean age was lower in the HIV group (p < 0.0001), the distribution of the genders did not show important differences between the two groups. The mean neutrophil count and mean leukocyte count was lower in the neutropenic group (p < 0.0001). The mean duration of fever and the mean duration of hospitalization were longer in the HIV group (p < 0.0001). The mean time until the establishment of diagnosis was longer in the HIV infected patients (p = 0.0019). A wide range of diagnostic methods were useful in the establishment of the cause of FUO in the HIV group, whereas in the neutropenic group the routine examinations such as blood cultures, chest x-rays were the most helpful. Mycobacterial infections were the major cause of fever in the HIV infected group, followed by other infections, tumors, miscellaneous causes, whereas FUO was caused by infections only (mainly sepsis and pneumonia) in the neutropenic group. The baseline disease was diagnosed more frequently during the investigations performed for FUO in the HIV infected group (36.2% versus 13.33%). Multiple causes of fever were found in 12.19% of the HIV infected group and in 9.09% of the neutropenic group. The antituberculous drugs, macrolides and quinolones were used more frequently in the treatment of the HIV infected patients with FUO. GCSF (granulocyte colony stimulating factor) was used more frequently in the neutropenic patients (40% versus 8.47%). The repetition of FUO was more frequent in the neutropenic group. The death rate at 1 month and 6 months was higher in the neutropenic group.

**Discussions:** Our results are similar with those published by other authors with regard to the baseline disease, diagnostic methods, causes of fever, the percentage of undiagnosed cases in the neutropenic group, the usage of empirical therapies, and repetition of FUO. The duration of fever, hospitalization and the time until the establishment of diagnosis were longer in this study than in other publications. The rate of undiagnosed cases was higher in the HIV infected group than found in the literature. The death rate was higher than that communicated by some studies, and lower than the results of other studies.

**Conclusions:** FUO is more frequent in the HIV infected patients with impaired immunological and virological status and in the neutropenic patients with acute myeloid leukemia. The duration of FUO, of hospitalization and the time until the establishment of diagnosis is longer in the HIV infected patients than in the neutropenic patients. The most helpful diagnostic method in the investigation of FUO in HIV infected patients is limphonodular histopathological examination, whereas in neutropenic patients it is the blood culture. The main cause of FUO is mycobacterial infection in the HIV infected patients and sepsis in the neutropenic patients. Multiple causes of FUO appear at similar rates in the HIV infected and neutropenic patients. The baseline disease is diagnosed more frequently during the investigations made for FUO in the HIV infected patients. The repetition of FUO is more frequent in the neutropenic patients. The death rate is higher in the neutropenic patients with FUO. HIV infected patients with FUO should be treated empirically for opportunistic infections and the antiretroviral therapy has to be revised. Neutropenic patients with FUO should be treated empirically with antibiotics, antifungals and GCSF.