**Abstract**

The aim was to evaluate the etiologies of Fever of Intermediate Duration (FID) in a prospective study performed at an Infectious Diseases Department in Spain (January 2005-August 2008 and January-July 2010). An infectious cause (62.50% bacteria and 37.50% viruses) was attributed in 77.67% cases, 4.85% were non-infectious cases, and for 17.48% the etiology was unknown. Using immunofluorescence assays (IFA, IgG) and/or PCR targeting 16S rRNA gene and\(\text{ompA}\) and\(\text{ompB}\) Brickettsial genes followed by sequence analysis, 33 patients (32.04%) showed evidence of spotted fever group Rickettsia infection (Mediterranean spotted fever). IgG antibodies against Coxiella burnetii were detected in 15/103 patients (14.56%) by IFA, and one serum sample showed IgG antibodies against Rickettsia typhi (0.97%). Francisella tularensis-specific antibodies were detected in 1/103 patients (0.97%) using microagglutination test. Based ELISA or chemiluminescence assays, Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) infections were the most frequent viral infections (12.62 and 9.71%, respectively), followed by Erythrovirus B-19 infection in 4/103 patients (3.88%) and Human Immunodeficiency Virus (HIV) acute infection in 3/103 patients (2.91%), respectively. In conclusion, Rickettsia spp. and C. burnetii were the most important etiological agents of FID. The empirical use of doxycycline could be appropriate since it is effective for most patients.

**ABBREVIATIONS**

FID: Fever of Intermediate Duration; MSF: Mediterranean Spotted Fever; HIV: Human Immunodeficiency Virus; EBV: Epstein-Barr Virus; CMV: Cytomegalovirus

**INTRODUCTION**

Fever is one of the most important signs that alert us of an infectious disease. Most books of Medicine distinguish between the terms short duration fever (mainly caused by self-limited viral or bacterial infections of the upper respiratory tract) and fever of unknown origin [1]. Nevertheless, there is a group of acute febrile illnesses that do not match with those previously mentioned. Thus, the term fever of intermediate duration (FID), coined in Spain, defines a clinical entity characterized by acquired-community fever higher than 38°C lasting 7-28 days that remains without diagnosis (or findings that suggest a diagnosis) after anamnesis, physical examination, hemogram, serum creatinine determination, urine analysis and chest X-ray [2]. The investigation of the etiologic causes of FID can be very useful to optimize the management of this clinical syndrome [2-6].

The aim of this study was to assess the etiologies of FID in patients admitted to the Department of Infectious Diseases, Hospital San Pedro in La Rioja (northern Spain).

**PATIENTS AND METHODS**

Patients with FID attended in an Infectious Diseases Department in a tertiary hospital were prospectively studied from January 2005 to August 2008 and from January to July 2010.
Inclusion criteria

Patients older than 14-year-old with the following FID criteria were included: a) fever higher than 38ºC without localized origin, with a duration from 1 to 4 weeks, b) no previous hospital admission or health care-related attention, c) no underlying immunodeficiency or any chronic disease that could cause fever; d) no diagnostic orientation after an initial approach including clinical evaluation, hemogram, urinary sediment, serum creatinine determination and chest X-ray. Patients with previously known Human Immunodeficiency Virus (HIV) infection, intravenous drug users, immigrants with less than a year of continuous residence in Spain or people who had travelled abroad in the previous 6 months, were excluded.

Study protocol and variables

For all patients, a basic evaluation including demographic data, full anamnesis, clinical signs and symptoms was performed. In addition, microbiological studies included blood cultures (Bactec 9240; Becton-Dickinson, USA), urine culture (Bactec-9240; Becton-Dickinson, USA), spleen, lung, liver, kidney, bone marrow biopsy, lymph nodes, conjunctiva, cerebrospinal fluid, and cerebellar tissue, when available. In those cases, the results were only useful for the medical history and the anamnesis, they were not included in the microbiological study of the specific case. Microbiological studies using nucleic acids amplification techniques were performed with patients’ blood, and sometimes with other samples when necessary (lymph nodes, conjunctiva, cerebrospinal fluid, urine, or cerebellar tissue) to confirm the presence of pathogenic microorganisms. Among the bacterial aetiologies, Mediterranean Spotted Fever (MSF) was the most common bacterial cause of FID (12.62% of the FID cases). These extracts were used as templates in PCR assays targeting the pan-bacterial 16S rRNA gene (or other specific PCR assays targeting specific bacterial genes when rickettsiosis was suspected). DNA sequencing and nucleotide sequence comparison with those available in GenBank was carried out.

RESULTS AND DISCUSSION

A total of 103 patients with an average age of 42.8 years (from 16 to 77) were included, and 80% of them were younger than 60-year-old. Sixty two per cent of them were male. The highest number of cases of FID were diagnosed in 2005 (n=33) and the lowest one, in 2006 (n=13). An infectious disease cause was attributed for 77.67% of the FID cases (62.5% by bacteria and 15.15% by viruses). Non-infectious causes (neoplasm, connective tissue, inflammatory or genetic diseases) accounted for 22.33% of FID cases, and 17.48% did not have an etiological diagnosis. Among the bacterial aetiologies, Mediterranean Spotted Fever (MSF) (32.04%) and Q fever (14.56%) were the most frequent causal diagnosis. The diagnosis of MSF was confirmed by PCR of ompA, ompB and 16S rRNA partial genes and sequencing in 5/33 cases (15.15%). Other bacterial infections were associated to tularaemia or murine typhus, with one case each. CMV and EBV infections (12.62 and 9.71%, respectively) were the most frequent viral infections, followed by Erythrovirus B-19 (3.88%) and acute infection by HIV (2.91%).

This clinical entity had higher incidence in spring (45%) and summer (19%) than in cold seasons. Nevertheless, the study design has bias due to the periods of collection of data. Thus, patients suffering from FID in autumn of years 2008 and 2010 were not studied. It is worth mention that MSF was more frequent in spring (May-June) than in summer (16%) or winter (8%). No cases of MSF were observed in autumn.

Currently, the aetiology of FID is not well defined. There are few studies about the clinical spectrum of FID [2,4,7-10], and the most extensive ones have been carried out in Andalusia (southern Spain) [2,7,9,10]. Up to our knowledge, there is only one study using the term FID out of Spain [11]. It is a case report of a patient suffering from fever, headache and maculopapular rash after returning to Germany from the Canary Islands [11].

According to the most recent data from the South of Spain, Q fever was the most common bacterial cause of FID [10]. However, brucellosis, a very frequent infection in the past decades, and MSF seem to be decreasing in that area respect to previous periods [2]. In our series, no cases of brucellosis were observed. Contrarily, MSF was the first cause of FID and Q fever was the second one. The same trend was observed in the two analyzed time periods. The availability of techniques for the study of intracellular microorganisms (Rickettsia and Coxiella, among others) outside the hospital routine (Center of Rickettsiosis and Arthropod-Borne Diseases) contributes to support the diagnosis of these diseases, and could justify the high prevalence of these bacteria in our region.

MSF is a tick-borne rickettsiosis caused by R. conorii. Patients usually present fever and exanthema with or without eschar and lymphadenopathies. Other Rickettsia species can cause similar syndromes called MSF-like [12]. These bacteria are obligate intracellular Gram-negative bacteria belonging to alpha 1 Proteobacteria (order Rickettsiales) that are transmitted by arthropods [13].

Q fever is a worldwide distributed zoonosis. The etiologic agent, C. burnetii, is a highly pleomorphic Gram negative coccobacillus included in the gamma group of Proteobacteria (order Legionellales) [14]. Most infections due to C. burnetii are asymptomatic. However, there are several acute clinical syndromes associated to C. burnetii infections, from self-limited febrile illness with or without hepatitis to pneumonia. Less frequent are cases of meningoencephalitis, pericarditis or myocarditis [15-17]. Some patients with underlying medical disorders such as cardiac valvular diseases or cancer develop chronic Q fever. In Spain, Q fever usually presents with fever, chills and headache that may be accompanied by pneumonia and/or hepatitis [18], and large series of patients with endocarditis have been published [19]. Besides, chronic forms of endocarditis associated to cardiac implantable electronic devices have been reported [20].

As previously stated by our group, PCR-based amplification methods are useful diagnostic tools in the early phase of infectious illnesses, such as rickettsiosis or blood culture-negative endocarditis [20,21]. The application of these molecular biological techniques for the detection of C. burnetii and Rickettsia spp. can be also helpful for the early diagnosis of the main causes of FID [22].
Following MSF and Q fever cases, infections caused by the herpes group viruses such as CMV and EBV, were the most commonly involved infections in our study. The infection by CMV has been with difference the most frequent diagnosis in the series from southern Spain [10].

Since the first reports about FID, the use of empiric doxycycline has been proposed for the management of this syndrome. With this approach, the majority of the aetiologic agents were well treated at low cost [2,3]. In the past decades, brucellosis could had been a problem since a combination of drugs for 6 weeks was necessary, but nowadays this infection is absent in our environment. The viral aetiology of FID could represent another problem. In our opinion, a correct re-evaluation 2-3 days after the onset of doxycycline prescription would allow us to select patients who would have to undergo specific assays for the diagnosis of viral infection. This clinical practice would save the costs of additional antibodies detection tests that require 2 or 3 weeks before knowing the aetiology. The proposal of an algorithm of treatment taking into account local differences, groups of age and, if possible, a marker to distinguish viral or bacterial infections would avoid discomfort to the patients and save money to the Public Health System [4].

CONCLUSION

Rickettsia spp. and C. burnetii are the most important agents of FID in La Rioja (North of Spain). These bacteria should be taken into account for the differential diagnosis of FID in our environment. A strategy using empirical doxycycline could be taken into account for the differential diagnosis of FID in our environment. The viral aetiology of FID could represent another problem. In our opinion, a correct re-evaluation 2-3 days after the onset of doxycycline prescription would allow us to select patients who would have to undergo specific assays for the diagnosis of viral infection. This clinical practice would save the costs of additional antibodies detection tests that require 2 or 3 weeks before knowing the aetiology. The proposal of an algorithm of treatment taking into account local differences, groups of age and, if possible, a marker to distinguish viral or bacterial infections would avoid discomfort to the patients and save money to the Public Health System [4].

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REFERENCES