Relapsing Fever Epidemiology in Spain According to Hospitalization-Based Records, 2004-2013

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Abstract

Introduction: Louse-borne and tick-borne relapsing fevers are infectious diseases caused by some species of Borrelia genus. The aim of this study was to describe the relapsing fever epidemiology in Spain and its Autonomous Communities during a decade.

Material and methods: An observational study was carried out, during the period 2004-2013, of those patients whose main or secondary diagnosis when discharged from hospital was encoded at the Minimum Basic Data Set (MBDS) according to the International Classification of Diseases 9th revision Clinical Modification (ICD-9-CM) with the codes 087,0 (tick-borne relapsing fever, endemic), 087,1 (louse-borne relapsing fever, epidemic) or 087,9 (relapsing fever not specified).

Results: During the research period, 349 admitted patients with discharged diagnosis of relapsing fever were diagnosed. The incidence rate was 0.808 cases per 1,000,000 inhabitants. The relative risk male/female was 1.37:1. The predominant age group was the range 0 to 4 years old (22.27%). In-hospital mortality rate was 0.4%.

Conclusion: Relapsing fever incidence in Spain is low. It has a clear predominance in the childhood, especially under the age of five and more incidence in male. In-hospital mortality rate was minimal.

ABBREVIATIONS

RF: Relapsing Fever; LBRF: Louse Borne Relapsing Fever; TBRF: Tick Borne Relapsing Fever; ND: Notifiable Disease; MBDS: Minimum Basic Data Set; DRG: Diagnostic Related Group; ICD-9-CM: 9th International Classification of Diseases 9th Revision Clinical Modification

INTRODUCTION

Relapsing Fever (RF) is an infectious disease transmitted by arthropod bites. It manifests as recurrent fevers (by repeated spirochaetemia) with two clinical forms: epidemic, transmitted by Ix (LBRF), and endemic, transmitted by soft ticks of the genus Ornithodoros (TBRF) [1].

Relapsing fever is an acute, potentially serious disease, caused by several species of gram-negative spirochaetes of the genus Borrelia, of which Borrelia hispanica is the predominant in the Iberian Peninsula and North Africa. The number of relapses is very variable (from one to five habitually), but its duration is becoming shorter and less intense, mostly ending with recovery [1].

Relapsing fever is probably the most common bacterial disease in Africa. LBRF can be found in areas of Africa and South America and in the form of endemic foci, in areas under conditions of poverty and social disintegration due to catastrophes and wars, favoring lice infestation [1]. In contrast, TBRF is distributed worldwide, with the exception of the southeastern parts of the Pacific [1]. The highest endemic risk in Europe is found mainly in the Iberian Peninsula and in countries in the Mediterranean area [2,3].

A wide variety of animals act as reservoirs of the disease, such as wild and insectivorous rodents, micro mammals and birds, squirrels, deer, pigs, snakes, turtles and bats [4]. Ticks acquire
spirochetes when fed on infected rodents. Ticks of the genus *Ornithodoros*, which can survive for long periods of time, prefer humid and temperate environments, as well as heights between 500 and 1800 m [1].

*Borrelia hispanica* is found in Spain, Portugal, Cyprus, Greece and North Africa. It has been isolated in *O. erraticus*, commonly found under meso mediterranean vegetation in southwestern Europe [4]. This species of tick habitually lives in the burrows of wild rodents, its natural host, or in old buildings. In Spain and Portugal, however, it has been adapted to bite domestic pigs that are kept in continuous grazing [5]. The disease caused by *B. hispanica* is one of the less severe TBRF, presenting neurological signs in less than 5% of the cases [6]. Currently the TBRF is a Notifiable disease (ND) in Spain, although it was not in all Autonomous Communities during our period of study [2].

Relapsing fever has been reported sporadically in Spain, probably with an underestimated incidence [3,7]. In Spain, it was estimated that most cases were found mainly in summer in rural areas such as Andalusia, Castile and León, and Extremadura [1], although the dynamic nature of zoonoses may have changed this perception.

The objective of this study was to analyze the epidemiological data of RF in Spain during the decade 2004-2013.

**MATERIALS AND METHODS**

An observational, retrospective study was conducted based on information from the minimum basic data set (MBDS) of the National Epidemiological Surveillance System for hospital admissions, managed by the Ministry of Health, Social Services and Equality of Spain.

The MBDS is a set of clinical and administrative variables created in a standardized way at the time of the patient’s discharge. The clinical codes of the 9th International Classification of Diseases 9th revision, clinical modification (ICD-9-CM) [9], were used during the study period. Data were analyzed for all hospital admissions whose main or secondary diagnosis, based on clinical judgment, had been coded in the MBDS as 087.0 (tick-borne intermittent fever, endemic), 087.1 (intermittent lice-borne fever, epidemic) or 087.9 (intermittent fever not specified). In the MBDS, the diagnoses made in primary care are not included.

The main diagnosis is described as the pathological process or circumstance that after the pertinent study and according to the clinician’s criteria is the cause of admission to the hospital, although during the patient’s stay, there might appear important complications and even other more severe diseases independent of the one that motivated the admission [9]. Secondary diagnoses are those that coexist with the main at the time of admission or develop throughout the hospital stay and influence the duration of the stay or the treatment administered. On the other hand, diagnoses related to previous episodes that do not affect the current admission are excluded [9].

Records with the same history, date of birth, sex and autonomous community were excluded. A patient treated in Spain with residence abroad was included. The incidence was calculated based on the autonomous community of residence.

The target population was the one corresponding to Spain and its Autonomous Communities and provinces during the period 2004-2013, obtained from the Spanish population census through the National Institute of Statistics taking the population as a stable dynamic, with an annual average of 43,197,684 inhabitants.

The incidence by sex and age was determined using as denominator the population of the corresponding sex and age in each case in Spain and its Autonomous Communities and provinces.

In calculations obtained from the age, date of admission, stay, cost, readmissions, and service that admitted the patient, only those patients in whom relapsing fever was the main diagnosis were taken into account.

In-hospital mortality rate, type of admission, number of readmissions, descriptive statistics of age, days of stay and cost were calculated. Periods of the year, years with higher incidence and the services that more frequently admitted cases of the disease were determined.

The average cost was calculated, according to the state standard for the registration of discharges of the general hospitals of the National Health System, as the average cost in euros of the cases, taking into account the Diagnostic Related Group (DRG).

The data obtained were coded and inserted into an Excel and SPSS v23 database, from which a frequency analysis of the cases was performed, calculating the descriptive and inferential statistical parameters for the variables of interest. To study the normality of the distributions of different variables, the Kolmogorov-Smirnov goodness-of-fit test was used. The comparison between the values of two qualitative variables was performed using the Chi square test. A significance level of less than 0.05 was accepted in bilateral contrast.

**RESULTS AND DISCUSSION**

349 records were obtained with the diagnosis of RF during the period 2004-2013 applying the exclusion measures referred to in the section of material and methods. RF was the main diagnosis in 247 records (70.77%), of which 234 (94.74%) were classified as unspecified relapsing fever, 9 (3.64%) as TBRF and 4 (1.14 %) as LBRF. In the remaining 102 (29.22%), the disease was a secondary diagnosis, containing 91 cases (89.2%) of unspecified relapsing fever, 4 (3.92%) of TBRF and 7 (6.86%) of LBRF.

Therefore, overall, we found 325 cases of unspecified relapsing fever (93.12%), 13 of TBRF (3.72%) and 11 cases of LBRF (3.15%) Table 1. Internal medicine admitted 117 cases (47.37%), followed by pediatrics in frequency that admitted 75 (30.36%).

More cases were diagnosed in 2009, with 44 patients (17.81%), and in 2013, with 41 (16.60%), with statistically significant differences with other years (p=0.05). The year with the least diagnoses was 2007 with 15 admissions (6.1%). The average number of cases in the period was 34.9 per year.

The incidence of diagnosed cases in Spain stood at 0.808 cases (95% CI 0.807-0.809) per 1,000,000 inhabitants and year in the
period between 2004-2013. Table 2 shows that the autonomous community with the highest number of cases was Catalonia with 114 (32.66%), followed by Andalusia with 76 (21.78%).

The highest annual incidence rates per 1,000,000 inhabitants were in the autonomous city of Ceuta with 2.68 cases, followed by Catalonia with 1.67 (Table 2). In contrast, the lowest incidence rates were the Balearic Islands with 0.1 and Castile and León with 0.12 cases per 1,000,000 inhabitants per year.

Table 1: Diagnosis of relapsing fever registered in MBDS.

<table>
<thead>
<tr>
<th>Diagnosis in MBDS</th>
<th>Total Diagnosis</th>
<th>Main Diagnosis</th>
<th>Secondary Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tick-Borne Relapsing Fever</td>
<td>13</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Louse-Borne Relapsing Fever</td>
<td>11</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Unspecified Relapsing Fever</td>
<td>325</td>
<td>234</td>
<td>91</td>
</tr>
<tr>
<td>Total</td>
<td>349</td>
<td>247</td>
<td>102</td>
</tr>
</tbody>
</table>

Table 2: Number of cases and incidences per Spanish autonomous communities and provinces during the period 2004-2013.

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Incidences (x 1000000 Inhab/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andalusia</td>
<td>76</td>
</tr>
<tr>
<td>Almería</td>
<td>2</td>
</tr>
<tr>
<td>Cádiz</td>
<td>25</td>
</tr>
<tr>
<td>Córdoba</td>
<td>3</td>
</tr>
<tr>
<td>Granada</td>
<td>1</td>
</tr>
<tr>
<td>Huelva</td>
<td>4</td>
</tr>
<tr>
<td>Málaga</td>
<td>12</td>
</tr>
<tr>
<td>Sevilla</td>
<td>28</td>
</tr>
<tr>
<td>Aragon</td>
<td>14</td>
</tr>
<tr>
<td>Huesca</td>
<td>1</td>
</tr>
<tr>
<td>Teruel</td>
<td>1</td>
</tr>
<tr>
<td>Zaragoza</td>
<td>12</td>
</tr>
<tr>
<td>Asturias</td>
<td>7</td>
</tr>
<tr>
<td>Balearic Islands</td>
<td>1</td>
</tr>
<tr>
<td>Canary Islands</td>
<td>4</td>
</tr>
<tr>
<td>Las Palmas</td>
<td>1</td>
</tr>
<tr>
<td>Santa Cruz de Tenerife</td>
<td>2</td>
</tr>
<tr>
<td>Cantabria</td>
<td>1</td>
</tr>
<tr>
<td>Castile and León</td>
<td>3</td>
</tr>
<tr>
<td>Burgos</td>
<td>1</td>
</tr>
<tr>
<td>León</td>
<td>1</td>
</tr>
<tr>
<td>Valladolid</td>
<td>1</td>
</tr>
<tr>
<td>Castile La Mancha</td>
<td>19</td>
</tr>
<tr>
<td>Albacete</td>
<td>4</td>
</tr>
<tr>
<td>Ciudad Real</td>
<td>7</td>
</tr>
<tr>
<td>Cuenca</td>
<td>1</td>
</tr>
<tr>
<td>Guadalajara</td>
<td>2</td>
</tr>
<tr>
<td>Toledo</td>
<td>4</td>
</tr>
</tbody>
</table>

At the provincial level, Lleida with 4.41 cases, followed by Ceuta (2.68) are examples of higher incidences. Las Palmas with 0.1 and Granada with 0.12 cases per 1,000,000 inhabitants and year are the lowest provincial incidences Figure 1.

Statistically significant differences (p <0.05) were found between Ceuta and Catalonia and Autonomous Communities such as the Basque Country, Galicia, Madrid or Navarre. In the case of the provinces, statistically significant differences (p <0.05) were found between Lleida and all other provinces with the exception of Ceuta and Girona. In La Rioja, no case was detected during the period 2004-2013.

Of the total number of patients, 199 (57.02%) were men, and 150 (42.98%) women. The relative risk between men and women was 1.37 (95% CI 1.11-1.69). The incidence rate for men and women was 0.935 (95% CI 0.934-0.936) and 0.685 cases (95% CI 0.683-0.686) per 1,000,000 inhabitants and year respectively during the study period. The highest incidence of the disease in males was detected in Melilla, with a rate of 2.9 cases (95% CI...
2.855-2.95) per 1,000,000 inhabitants per year, and in females was detected in Ceuta with an annual incidence of 5.47 cases (95% CI 5.42-5.52) per 1,000,000 inhabitants and year.

The predominant age group corresponded to people between 0 and 4 years old with 55 cases (22.27%), followed by the age range of 5 to 9 years with 18 cases (7.29%).

The incidence of the age range 0-4 years was 2.79 cases (95% CI 2.76-2.81) per 1,000,000 inhabitants per year (Figure 2). The median age was 30 years with a range of 0-92 years. The mode was 1 and 2 years with 16 cases at each age. The inter quartile range was 56 years (Q1 6 years and Q3 62 years). Statistically significant differences (p <0.05) were found between the incidence of the 0-4 age group and all age groups.

There were incomes every month of the year. March stood out with 30 cases (12.15%) followed by July and August, with 25 cases both (10.12%). In the summer, 68 cases (27.53%), in winter, 65 cases (26.32%), in spring, 62 cases (25.1%) and in autumn, 52 cases (21.05%) were recorded, with no statistically significant differences.

The crude in-hospital mortality rate was 0.4% (95% CI 0.07-2.26%). Only one patient of 64 years died after an urgent admission and having as only diagnosis the unspecified relapsing fever.

195 patients (78.95%) were urgently admitted, compared to 52 (21.05%) who were admitted on a scheduled basis. The majority (81.38%) did not need a second reentry. The median stay was 5 days, with a range of 0 to 44 days, and the mode was 4 days (16.6% of patients). The inter quartile range was 5 days (Q1 3 days and Q3 8 days).

Seven cases with neurological symptoms such as meningitis, convulsions, Bell's palsy, hemiplegia and paralytic syndromes were diagnosed as concomitant diagnosis of RF. We recorded two neonatology cases with multiple respiratory, metabolic and neurological symptoms, which generated a high suspicion of possible transplacental transmission.

The majority of cases (108 cases, 43.72%) obtained a Spanish Weight Value of 0.8528. The median was 0.8528, with a range of 1.8598 (0.238-2.0978). The inter quartile range was 0.0022 (Q1 0.8506 and Q3 0.8528). The median cost was 3994.97€. The range was 8234.66 €, the inter quartile range was 657.48 € (Q1 3538.14 and Q3 4195.62). The maximum expenditure was recorded at the age of 77 years (9224.64 €) and the minimum at 0 years (989.98 €).

Almost all cases were classified in the DRG as 423 "other diagnoses of infectious and parasitic disease" (230 cases, 93.11%). Those who did not have this classification were located in 580 "Systemic infections and parasitic diseases except septicemia with major complication or comorbidity" (9 cases, 3.64%) or 415 "Surgical procedure for infectious and parasitic diseases" (5 cases, 2.02%).

Based on the severity level, that classified the diseases in four levels (minor, moderate, major and extreme), the majority of cases obtained grade 2 or moderate (218 cases, 90.83%), the highest grade was 3 or major, where we found 19 cases (7.92%), of which one was caused by LBRF (5.26%) and none by TBRF.

According to the classification by mortality risk level (using the same classification system as the severity level), the majority had a level 1 or minor (205 cases 85.42%). The highest mortality was recorded in 6 cases (2.5%) with a grade 3 or major, not including at this level any cases of TBRF or LBRF.
The estimated incidence for the period 2004-2013 of 0.8 cases per million inhabitants per year is lower than that reported in previous studies for Spain [1,10]. The incidence numbers in other areas of the world are variable. Thus Iran reported 0.06 cases per 100,000 inhabitants per year [11]. In the western region of Africa where this disease is hyperendemic, incidences of 11 cases per 100 inhabitants-years have been estimated (range from 4 in 1990 to 25 in 1997) [12]. In a Senegal incidence study after pre-prevention (pre) and post-prevention (post) data were obtained from 10.55 (pre) to 2.63 (post) cases per 100 inhabitants per year in Dielmo and from 3.79 (pre) to 1.39 (post) cases per 100 person years in Ndiop [13].

The male-female relative risk was higher in men as in other series [12]. 57% were men in the present study, the same proportion as Forrester et al., in the USA [14], and similar to the 56% calculated by Castilla-Guerra et al., in Andalusia [3], the 52% reported by Ayazi in Iran [15] or the total number of refugees arriving in Spain diagnosed with this disease [16].

As in other series analyzed, pediatric age was the most affected, specifically the range between 0 and 4 years [11] (with predominance in 1 and 2 years) with 22.27% of the total cases. That age range (0-4 years) was the most affected also in the study of Masoumi et al., in Iran with 33% of the total cases [11]. A lower percentage of cases (36.43%) were found in patients younger than 15 years of age, than calculated by Ramos et al., in Ethiopia (62.1%) [17]. In the same group of patients, the average was 4.98 years, compared to the average of 8.9 years in Addis Ababa [18]. In Tanzania, an incidence of 384 per 1,000 children fewer than 1 year of age and 163 per 1,000 children below 5 years of age was estimated [19].

The estimated median age was 30 years (range 0-92) similar to the 33-year mean calculated by Castilla-Guerra et al., (range 14-72) [3] and to the 38-year median calculated by Forrester et al., (range 1-91) [14].

The low lethality of this disease [11] is confirmed by obtaining a single case of death in a 64-year-old woman diagnosed with unspecified relapsing fever and without other secondary diagnoses. Previous studies have estimated mortality to be between 2 and 5% for TBRF and between 4 and 40% for LBRF. In the treated cases, mortality would decrease to less than 5% in both forms [1,20]. Castilla-Guerra et al., does not record any deaths in their 75 patients [3], nor does Croche Santander et al., in their pediatric patients [10]. Vial et al., in Senegal, does not registrar deaths during 14 years of study [12]. Nevertheless, in Ethiopia in 2004, LBRF was the fifth cause of mortality with 42 deceased patients (0.9%) [20].

The calculated incidences may be underestimated due to the nature of the study (observational – hospital based records) and because is a rare disease with nonspecific symptoms [3] and not include primary care cases in this study. The true incidence rate could be obtained by using a prospective study and a sensitivity test as PCR diagnosis technique that could tell the actual infections. Even more, PCR based on a flagellin gene has been shown to be suitable for both detection and classification of the genus [21,22].

It will be interesting to know the estimates of the TBRF in the coming years as it has recently spread throughout Spain the consideration of this disease as Notifiable disease (to date it was only in several Autonomous Communities such as Andalusia, Aragon, Castile and León, Valencian Community, Cantabria, Extremadura, La Rioja, Balearic archipelago and Canary and Melilla).

The cases detected through the MBDS (349 cases) were superior to those of National Network of Epidemiological Surveillance (RENAVE) (90 cases in the same period of time). RENAVE is a specific source of microbiological information but biased due to the willingness of microbiology laboratories to submit their diagnoses. In contrast, the MBDS are more sensitive to include all cases diagnosed at discharge from specialized care, although its specificity may be limited by the accuracy of clinical judgment.

It is noteworthy that the regions with the highest incidence were Ceuta and Catalonia, while we recently considered the main areas to be those of Andalusia, Castile and León and Extremadura [1]. The publications on relapsing fever and its epidemiology in Spain are scarce [3,7,10]. Two studies in the south of Spain showed their presence in this area and their under diagnosis due to their non-specific symptomatology and low clinical suspicion.
[3,10]. Regard the two zones of higher incidence, Ceuta and Catalonia, in Catalonia, RF, was not a ND in the period studied, instead in Ceuta, there are records of RF as ND since 2011. It will be interesting to know in future works if the high incidence of Ceuta is due to being endemic zone or to possible migratory movements.

Cases with neurological manifestations (meningitis, convulsions, Bell's palsy, hemiplegia and paralytic syndromes) were detected as concomitant diagnosis of RF, although MBDS does not allow quantification of its frequency [3,23]. A neonatology case was registered, with multiple respiratory, metabolic and neurological symptoms, leading to suspicion of transplacental transmission [24].

It is considered that the seasons of summer and autumn are those of greater incidences perhaps by the greater number of tick bites [1,11,15]. However, no statistically significant differences were found between the seasons, although the majority of the cases in the studied population were diagnosed in the months of March, July and August.

There are 11 cases of LBRF from the Autonomous Communities of Andalusia, Catalonia, Valencia Community, Madrid, the Canary Islands and Ceuta. This variety of RF is typical of crampd and warring sites [1,25] and the MBDS does not allow detecting whether cases were imported. Historically there were two major epidemics of RF in the twentieth century during the first and Second World War. These caused a total of 60,000 deaths and more than 2 million people affected between Egypt, Tunisia, Algeria and Morocco, and later extended to other African countries [20]. The current increase in immigration from both Asian and African countries with war or extreme poverty [10], could increase cases of RF in Europe [3].

CONCLUSION

Despite the limitations of the MBDS, this data source indicates that the incidence of relapsing fever in Spain is low, has a clear predominance in childhood, a higher incidence in men and minimum in-hospital mortality.

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