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Jarisch–Herxheimer Reaction Among Patients with Leptospirosis: Incidence and Risk Factors

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Abstract. A Jarisch–Herxheimer reaction (JHR) may be precipitated after initiation of chemotherapy in spirochetal diseases, including leptospirosis. However, a clear idea of the importance of JHR in this disease is lacking. The incidence of and risk factors for JHR were investigated retrospectively among 262 patients with confirmed leptospirosis who received amoxicillin treatment in New Caledonia and Futuna. The overall rate of JHR was 21% (12% in New Caledonia and 44% in Futuna). Two risk factors were independently associated with JHR occurrence: *Leptospira interrogans* serogroup Australis as the infecting strain (odds ratio [OR] = 2.60, confidence interval [CI] = 1.40–5.62) and delays < 3 days between the onset of symptoms and the initiation of antibiotherapy (OR = 2.14, CI = 1.11–4.38). Clinicians should be aware of JHR as a potential complication of leptospirosis. Strain-related factors associated with JHR occurrence and its impact on outcome remains to be explored.

INTRODUCTION

Leptospirosis is recognized as the most widespread zoonosis with more than 500,000 severe cases occurring every year worldwide.[1] Conditions for transmission are most favorable in tropical areas, including New Caledonia and Futuna, where leptospirosis is a significant public health problem.[2,3] New Caledonia and Futuna are both overseas French-administered territories located in the South Pacific, east of Australia.

In accordance with current treatment guidelines, the management of leptospirosis relies on antibiotic administration regardless of stage or severity of the disease.[4] Initiation of chemotherapy in spirochetal diseases may precipitate a febrile inflammatory reaction, known as the Jarisch–Herxheimer reaction (JHR), originally described in patients with syphilis receiving mercury treatment.[5,6] This reaction is characterized by an acute inflammatory response with release of large amounts of cytokines as a result of exposure to antigen released from lysis during a high-quantity spirochetemic phase of infection.[7,8] Contrary to syphilis,[9] Lyme disease,[10] tick-born relapsing fever,[11] and louse-born relapsing fever,[12] the overall rate of JHR for leptospirosis is not well documented.[13] In addition, factors associated with this complication are not clearly established. In this study, we aimed to investigate the incidence of and risk factors for JHR among patients admitted for leptospirosis in two Pacific islands after receipt of amoxicillin.

METHODS

We carried out an observational retrospective study among patients with a biologically confirmed leptospirosis admitted between January 2007 and December 2009 in either of two public hospitals (Center Hospitalier Territorial, Noumea, and Center Hospitalier du Nord, Koumac) in New Caledonia or in the single medical center in Futuna. Outpatients testing results for leptospirosis or patients with antibiotic treatment received before admission without clinical monitoring were not included in the analysis. Leptospirosis was defined by a compatible clinical syndrome (any combination of fever, chills, myalgia, jaundice, conjunctival suffusion, renal failure, hemorrhage, or pulmonary failure) and laboratory confirmation with one or more of the following features: 1) positive results for a microscopic agglutination test (using a panel of 11 serovars) and one acute-phase serum sample titer > 1:800, 2) seroconversion between times of testing acute- and convalescent-phase serum samples, 3) a 4-fold increase in titers between two examinations, or 4) a positive polymerase chain reaction (PCR).

JHR was defined as the combination of sudden onset of shivering or rigors, with rise in temperature, with or without a fall or a rise in blood pressure, increase of respiratory rate occurring within 6 hours after administration of the first dose of antibiotics and resolving within 24 hours. A 20% threshold change in hemodynamic or respiratory parameters was used. Since usual clinical presentation of leptospirosis includes nonmeasurable signs such as headache and myalgia, our JH definition differed from that suggested in guidelines for syphilis.[14,15] To detect early any deterioration, clinical monitoring of patients early after administration of antibiotics for suspected leptospirosis is common practice in New Caledonia and Futuna and data are reported in patients' notes. In practice, temperature, blood pressure, and respiratory rate measurements were taken every 2 hours for 6 hours and then every 6 hours for 24 hours.

Ethics statement. The study was approved by the Institutional Review Board of Center Hospitalier Territorial. Informed consents were not obtained from the patients as this was a retrospective study. All data were anonymized.

Statistical analysis. STATA (Stat Corp., College Station, TX) was used for analysis. Quantitative and qualitative variables were compared by using paired Student's t and χ^2 tests, respectively. When the frequency of events was five or values did not follow normal distributions, Fisher's Exact and Mann–Whitney tests were used. Logistic regression was used to identify factors associated with JHR and to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between exposure variables and JH cases. Interactions were sought by introducing interaction terms in the logistic regression model and testing for their significance at the 0.05 level.

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RESULTS

During the study period, 262 patients with confirmed leptospirosis who received antibiotic treatment were included in New Caledonia (N = 191) and Futuna (N = 71). The demographic characteristics of patients with leptospirosis and the clinical presentation of JHR were similar in New Caledonia and Futuna (Table 1). The overall incidence of JHR was 21% (95% CI = 18–30) with a higher incidence in Futuna (44%) compared with New Caledonia (12%) ($P < 0.001$). The spectrum of JHR is shown in Table 1. The median time to development of JHR was 4 hours (interquartile range = 2–5 hours) for the two groups. Fever resolved within 1–4 hours (spontaneously or with antipyretics).

Both microscopic agglutination test and PCR were used to identify the infecting serovar in 217 patients (83%). The most common sequence cluster type identified was linked to serogroup icterohemorrhagie in 71 patients, Australis in 70, Pyrogenes in 18, Bataviae in three, Ballum in two, and Pomona in two. Using MAT results, the serogroup involved was identified in 53 patients. Among these, 45 were confirmed cases with an acute and a convalescent serum and eight had a single MAT titer $\geq$ 1,600. The most common serogroups were icterohemorrhagie observed in 23 patients, Australis in 21, Pyrogenes in three, Panama in one, Pomona in one, Tarassovi in one, and Canicola in one. For the 45 remaining cases, identification of the serogroup was not possible.

Comparison of clinical and biological characteristics of patients in New Caledonia and Futuna is shown in Table 2. None of the patients treated in Futuna required intensive care. There was no statistical difference among 18 patients transferred to intensive care unit in New Caledonia, with or without JHR (OR = 0.89, CI = 0.69–1.02). Renal failure and thrombocytopenia were not associated with JHR occurrence. Patients who developed JHR following the first dose of amoxicillin did not have recurrent symptoms after the second dose during the same course of treatment. The pregnancy status of women having JHR was not known, except for one who was obviously pregnant. The outcome was favorable both for the mother and the fetus.

Two risk factors were independently associated with JHR occurrence: *Leptospira interrogans* serogroup Australis as the infecting strain (OR = 2.60, CI = 1.40–5.62) and delays < 3 days between the onset of symptoms and the initiation of antibiotherapy (OR = 2.14, CI = 1.11–4.38) (Table 3).

DISCUSSION

This retrospective case–control study of leptospirosis allowed us to identify risk factors associated with JHR in two Pacific Islands. One major finding of our study was the independent association between the serogroup Australis and occurrence of JHR. Although various strains were identified in JHR in previous reports, none were clearly associated with this complication. Hypotheses regarding JHR occurrence were based more on host genetic susceptibility factors rather than bacterial characteristics. The more prevalent strain in Futuna during the study period was Australis serogroup, tied to pig farming and causing few severe cases.[3] Our finding requires further research to better characterize strain-dependent factors potentially triggering JHR.

Multivariate analysis identified another risk factor linked to the initial management of the disease: if antibiotics were started earlier than 2 days after symptom onset, the risk of developing a JHR was higher than if antibiotics were started later on. Early antimicrobial therapy initiation in suggestive epidemiological and clinical contexts is recommended, even before laboratory confirmation of leptospirosis.[4,16] The present association with delay, which has also been found for syphilis[9] underscores the need for monitoring patients when initiation of antimicrobial therapy occurs early in the course of the disease. Leptospiremia was not observed for most patients and therefore potential association between bacterial load and JHR occurrence could not have been analyzed. Although time from onset of symptoms to treatment was similar in both islands, a higher leptospiremia in cases treated in Futuna has possibly contributed to the observed difference in JHR incidence. Since a higher load of spirochetes in the early stages of syphilis increases the risk of JHR when patients receive bactericidal agents,[9] this aspect needs to be explored in leptospirosis.

The proportion of JHR was high in our study, suggesting that suspected cases of leptospirosis should be systematically

TABLE 1
Clinical characteristics of patients admitted with confirmed leptospirosis, 2007–2009

Characteristics	Total N = 262	New Caledonia N = 191	Futuna N = 71	P
Age, mean ± SD (years)	35 ± 10.7	36 ± 12.1	34 ± 9.1	0.9
Male sex	206 (79)	150 (79)	56 (71)	0.95
JHR	54 (21)	23 (12)	31 (44)	< 0.001
Type of reaction				
Shivering/rigors with rise in temperature	54 (100)	23 (100)	31 (100)	0.95
Fall in blood pressure	26 (48)	11 (49)	15 (47)	0.85
Rise in blood pressure	20 (37)	8 (33)	12 (40)	0.08
Increase of respiratory rate	45 (83)	20 (89)	25 (78)	0.09
Onset of JHR following amoxicillin treatment, hours (IQR)	4 (2–5)	4 (2–5)	4 (2–5)	0.95
Infecting serogroup (N = 217)				
Icterohemorrhagie	94/217	89 (95)	5 (5)	< 0.001
Australis	91/217	32 (35)	59 (65)	0.01
Other	32/217	20 (62)	12 (38)	< 0.001
Laboratory identification method				
PCR	164/217	132 (61)	32 (19)	
MAT	53/217	33 (62)	20 (38)	
Transfer to intensive care	18 (100)	18 (9)	0	

JHR = Jarisch–Herxheimer reaction; IQR = interquartile range; PCR = polymerase chain reaction; SD = standard deviation.

TABLE 2
Univariate analysis of factors associated with JHR among patients with confirmed leptospirosis, New Caledonia and Futuna, 2007–2009

Variable		JHR $N = 54$	No JHR $N = 208$	OR (95% CI)	P
Gender	Female	19 (37)	79 (38)	1	
	Male	35 (63)	129 (62)	0.94 (0.50–1.75)	0.84
Age (years)	Mean (SD)	30 (8.5)	16 (14.5)		
	≤ 30	33 (61)	131 (63)	1	
	> 30	21 (39)	77 (37)	1.37 (0.68–2.77)	0.29
Infecting serogroup	Other	1/40 (2)	11/177 (7)	1	
	Icterohemorrhagie	6/40 (15)	98/177 (55)	0.35 (0.10–0.59)	0.003
	Australis	33/40 (83)	68/177 (38)	2.75 (1.30–5.82)	0.008
Delay between onset of symptoms and initiation of antibacterial therapy (days)	> 2	18 (33)	97 (47)	1	
Creatinine (mm/L)	0–2	36 (67)	110 (53)	2.24 (1.21–4.17)	0.01
	≤ 200	40 (74)	170 (82)	1	
Platelet count (g/L)	> 200	14 (26)	38 (18)	1.67 (0.80–3.50)	0.17
	≤ 50	13 (36)	70 (34)	1	
Transfer to intensive care	> 50	41 (74)	137 (66)	1.44 (0.73–2.82)	0.29
		1 (2)	15 (7)	0.89 (0.69–1.02)	0.07

CI = confidence interval; JHR = Jarisch–Herxheimer reaction; OR = odds ratio; SD = standard deviation.

monitored when receiving the first dose of bactericidal agents. JHR is not classically reported in studies describing prognostic factors of leptospirosis but clinicians are usually facing complicated management.[17,18] Moreover, although the JHR is usually self-limited, the reaction might be severe enough to result in cardiovascular failure with potential aggravation of renal damage. Interestingly, all cases in Futuna were treated successfully where neither intensive care nor dialysis is available, whereas 10% of patients admitted in New Caledonia required secondary transfer to intensive care unit, most of them without JHR. Laboratory findings known for their strong correlation with severe outcomes, including renal failure and thrombocytopenia were not associated with JHR occurrence in our study. The association between JHR and renal injury should be formally assessed in a prospective study.

Since laboratory methods of confirmation provide delayed results or are even not widely available in resource-limited settings where leptospirosis is prevalent, reliance is placed on clinical features for provisional diagnosis. However, the clinical presentation of the disease is known to mimic the clinical profile of other prevalent tropical fevers. Our finding suggests that JHR occurrence in patients presenting with suspected leptospirosis in Australis serogroup prevalent area may serve as an early sign predicting leptospirosis. This clinical observation may usefully complete a model recently elaborated for diagnosis of leptospirosis, based on clinical features and standard laboratory test results.[19]

Our study has several major limitations. First, the retrospective design exposed to misclassification bias, including patients with early recovery, or compensated severe sepsis, a prospective data collection for our definition would be more rigorous. Second, the definition for JHR was based on clinical signs and not supported by any level of biological markers. Therefore, although most of the cases presented a genuine JHR, some might have had a clinical aggravation related to the spirochetal disease regardless of the antibiotherapy. In addition, we cannot exclude that chills and increase fever were not part of leptospirosis disease after the weaning off of the effect of antipyrexial drugs. Third, the sample size of our study remains small, which limits our subgroup analyses in attempts to identify other factors for JHR, such as ethnicity. Fourth, deciding the infecting serogroup based on MAT is having a very low sensitivity and difficult to use as a predictor. Finally, although multivariate analysis supports an association of serovar with JHR, potential host, pathogen, environmental, and clinical confounding features may exist between the two sites.

In conclusion, JHR in leptospirosis is not rare in the Pacific and deserves full attention from clinicians treating suspected leptospirosis cases. *Leptospira interrogans* serogroup Australis and short delays between the onset of symptoms and the initiation of antibiotherapy are associated with an increased risk for JHR. Strain-related factors associated with JHR occurrence and severity and its impact on outcome remain to be explored.

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TABLE 3
Multivariate analysis of independent factors associated with JHR among patients with confirmed leptospirosis, New Caledonia and Futuna, 2007–2009

Variable		JHR $N = 54$	No JHR $N = 208$	OR (95% CI)	P
Infecting serogroup	Other	7/40 (17)	109/177 (62)	1	
	Australis	33/40 (83)	68/177 (38)	2.60 (1.40–5.62)	0.009
Delay between onset of symptoms and initiation of antibacterial therapy (days)	> 2	18 (33)	97 (47)	1	
	0–2	36 (67)	110 (53)	2.14 (1.11–4.38)	0.01

CI = confidence interval; JHR = Jarisch–Herxheimer reaction; OR = odds ratio.

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