The Seasonality, Steroid and the Lower Ratio of Neutrophil to Lymphocyte Associated With Listeriosis in Japan

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Research Article

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Abstract

Background: Although listeriosis is a foodborne infection with a high mortality rate, studies of listeriosis from Asia are limited. We aimed to compare the characteristics of listeriosis and non-listeriosis (defined as bacteremia without *Listeria monocytogenes* infection) in Japan.

Methods: We conducted a case–control study of adults with listeriosis or with bacteremia without *L. monocytogenes* infection from January 1, 2010, to December 31, 2019, at Tokyo Medical University Hospital in Japan. We recorded the incidence of admissions and the clinical characteristics, including age and sex; underlying disease; clinical symptoms; onset month; whether listeriosis was community-associated or health care–associated; medicine; blood count; biochemical findings; antibiotics use; admission to the intensive care unit; and outcome.

Results: A total of 12 patients were included in the case group and 28 patients were included in the control group. Most cases of listeriosis were present in patients of an advanced age, with underlying disease, and/or on immunosuppressant therapy. Two patients died within 30 days and one developed a brain abscess. Listeriosis onset was associated with the warm season (90.9% vs. 53.8%; $P = 0.033$), steroid use (54.5% vs. 19.2%; $P = 0.042$), and a lower ratio of neutrophils to lymphocytes (9.46 vs. 18.44; $P = 0.015$).

Conclusion: The incidence of listeriosis in this study was similar to that in other Asian countries and the 30-day mortality rate was 18.2%. We observed that listeriosis onset was associated with the warm season, steroid use, and a lower ratio of neutrophils to lymphocytes.

Background

Listeria monocytogenes is a ubiquitous Gram-positive rod in the environment. The invasive infection caused by *L. monocytogenes*, which can lead to bacteremia and meningitis, is called listeriosis. Listeriosis has generally been recognized as a foodborne infection that develops outside the hospital. Several outbreaks attributable to a variety of foods were reported over the past few decades [1–5]. Although the incidence per 100,000 people as a foodborne illness is lower than that of other pathogens like *Campylobacter* sp., *Salmonella* sp., and *Shigella* sp., rates of hospitalization and death due to listeriosis are high in the United States [6–9]. Conversely, two studies of listeriosis from China suggested that high mortality rates exist among adults [10, 11]. Some sporadic cases from Japan have also appeared in the literature since the first case of human listeriosis was reported in the country in 1959 [12], but, overall, adequately described studies of listeriosis in Asian populations that focus on risk factors, symptoms, hematological examinations, and outcomes are more limited than those from Western countries, in part due to underreporting [13]. We therefore aimed to investigate the characteristics of listeriosis, including the incidence, distribution of onset month, mortality rate, and factors associated with this condition, in a Japanese population.

Methods

We conducted a case–control study of adults with listeriosis or bacteremia without *L. monocytogenes* infection from January 1, 2010, to December 31, 2019, at Tokyo Medical University Hospital (TMUH), which is a 1,015-bed university tertiary hospital located in Tokyo, Japan. The study population included all hospitalized patients. Patients with listeriosis were defined as those with bacteremia of *L. monocytogenes* detected by blood culture. Controls were patients with bacteremia caused by organisms other than *L. monocytogenes* determined by blood culture and were selected according to age, diagnosis, and treatment department to match each case of listeriosis. Exclusion criteria were patient under the age of 18 years, contamination, refusal to join the study, and insufficient medical records. We examined the incidence of admissions for observation and the clinical characteristics—including age and sex; underlying disease; clinical symptoms; onset month; whether listeriosis was community-associated or health care–associated; steroid, immunosuppressant, and/or acid inhibitor use; oral iron; blood count, including the ratio of neutrophils to lymphocytes; biochemical findings following blood testing; antibiotics use; admission to the intensive care unit; and outcome—were collected by a review of the medical records.

Blood cultures were performed using the BACTEC FX system (Becton, Dickinson, and Co., Franklin Lakes, NJ, USA), and strains were identified with the MicroScan WalkAway-96 (Beckman Coulter Inc., Brea, CA, USA) and microflex LT/SH (MALDI Biotyper; Bruker Corporation, Billerica, MA, USA) systems. Infectious disease doctors in TMUH confirmed the presence of contamination based on the presence of coagulase-negative *Staphylococcus* sp. or indigenous bacteria like *Bacillus* sp. or *Corynebacterium* sp. in just one out of two blood cultures without clinically sufficient evidence of medical attention. The entry of causative microorganisms was identified by infectious disease doctors. Health care–associated bacteremia was defined if the onset of bacteremia occurred at least 48 hours after admission, while community-associated bacteremia was defined if the onset occurred before 48 hours after admission. The warm season was defined as the period of May to October and the cold season was defined as the period of November to April after collecting the dates of onset month.

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows, version 26 (IBM Corporation, Armonk, NY, USA). The test of normality was performed using the Shapiro–Wilk test. Group comparisons were performed using two-sample *t*-tests and Welch’s test for normally distributed continuous variables and the Mann–Whitney *U* test for non-normally distributed continuous variables. Differences in proportions were compared using a chi-squared test and Fisher’s exact test. A significance threshold of 0.05 was adopted for all statistical analyses.

This study was approved by the TMUH institutional review board (approval no. T2020-0379); after obtaining this approval, we disclosed this study to patients on the TMUH homepage and created an occasion to refuse joining to this study.

Results

There were a total of 236,689 admissions over 10 years to TMUH. Twelve patients were selected for inclusion in the case group and 28 patients were identified for inclusion in the control group; however, one neonate was later excluded from the case group and two patients were excluded from the control group because one was identified as a contamination case and one had insufficient clinical information. Thus, 11 patients were finally included in the case group and 26 were included in the control group. The incidence of listeriosis was 0.51 per 10,000 admissions to TMUH.

The clinical characteristics of the case group are shown in Table 1. Underlying diseases included constipation (n = 6), chronic kidney disease (n = 3), autoimmune disease (n = 3), solid tumor (n = 3), hematologic malignancy (n = 3), intravascular device (n = 3), diabetes (n = 2), hepatitis C (n = 2), and cirrhosis (n = 1). Seven cases were taking immunosuppressant drugs like steroids and/or methotrexate. Two cases presented with complicated central nerve system infections, including one with meningitis and one with a brain abscess. The involved clinical departments consisted of the departments of neurosurgery, neurology, cardiology, nephrology, respiratory medicine, urology, and rheumatology. The distribution of onset month among the 11 cases is shown in Figure 1 and, notably, 10 cases of listeriosis had developed during the warm season. Cephalosporins to which *L. monocytogenes* is inherently resistant to were administered in five cases as initial empiric therapy; one case without initial empiric therapy progressed to meningitis and two of the five cases died. The 30-day mortality rate in the listeriosis group was 18.2%.

The causative microorganisms in the control group were *Staphylococcus aureus* (29.6%), *Escherichia coli* (18.5%), *Klebsiella pneumonia* (11.1%), *Enterococcus faecalis* (11.1%), coagulase-negative *Staphylococci* (11.1%), extended-spectrum β -lactamase-producing *enterobacteriaceae* (11.1%), *Pseudomonas aeruginosa* (3.7%), *Enterobacter aerogenes* (3.7%), *Serratia marcescens* (3.7%), and group B *streptococci* (3.7%).

Case and control patients were compared to calculate the odds ratios of clinical characteristics (Table 2). The onset of listeriosis cases was statistically significantly more frequent in the warm season than in the cold season as compared with (control) non- listeriosis infection cases (90.9% vs. 53.8%; $P = 0.033$). Underlying diseases did not differ between the groups, but more patients with listeriosis were taking steroids (54.5% vs. 19.2%; $P = 0.042$). Although the mean counts of neutrophils and lymphocytes were not different between the groups, the ratio of neutrophils to lymphocytes was lower in the listeriosis case group than in the control group (9.46 vs. 18.44; $P = 0.015$). The unknown entry of offending bacteria was higher in patients with listeriosis than in those without listeriosis (100.0% vs. 34.6%; $P < 0.001$). The 30-day mortality rate of the listeriosis case group was similar to that of the control group (18.3% vs. 19.2%; $P = 0.619$).

Discussion

In this study, we found that the incidence of listeriosis was 0.51 per 10,000 admissions to TMUH and the 30-day mortality rate was 18.2%. Moreover, listeriosis onset occurred more often in the warm season than

in the cold season and in patients using steroids and/or with a low ratio of neutrophils to lymphocytes.

To our knowledge, this study is the first case–control study to compare cases of listeriosis and non-listeriosis, defined as bacteremia without *L. monocytogenes* infection. In Asia, especially in Japan, studies of characteristics of listeriosis are limited. A nationwide survey conducted between 1980 and 2002 in Japan reported that the incidence of *L. monocytogenes* infection was 0.65 cases per one million people [14], although the incidence per 10,000 admissions is unclear because listeriosis is not designated as an infectious disease of concern in Japan. A study from Taiwan in 2015 reported that the incidence of listeriosis is 1.25 per 10,000 admissions [15], while one from Korea in 2018 reported that the incidence of listeriosis was 0.31 per 10,000 admissions [16]. Also, a pediatric study from Singapore reported that the incidence of listeriosis in newborns was 0.48 per 10,000 live births [17]. Our incidence of listeriosis, recorded as 0.51 per 10,000 admissions at TMUH, is similar to these prior Asian reports.

The study of the season of onset of listeriosis is poor and results are variable. One study from Taiwan reported that more than 36.7% of patients acquired invasive listeriosis in the spring [15], While research from England and Wales reported that summer was the predominant season of listeriosis onset [18]. In Israel, the incidence in nonperinatal women was 64.2% in the hot season (May–October) [19]. A study from France documented an increase of cases during the summer [20]. Our study also contended that listeriosis occurs more frequently in the warm season. The reason for increased numbers of listeriosis cases in the hot or warm season is unclear, although Vasilev et al. hypothesized that there is a link with the concomitant increase in gastrointestinal infection [19]. Although *L. monocytogenes* infections were more prevalent during the warmer season in a cold-smoked fish processing plant in Japan [21], the seasonality of foodborne listeriosis is unclear. More epidemiological investigation of listeriosis is needed.

The MONALISA study reported that the mean counts of total leucocytes and blood polymorphonuclear cells were 10,920/ μ L and 8,400/ μ L in patients with bacteremia caused by *L. monocytogenes* [6]. However, no study of the ratio of neutrophils to lymphocytes in patients with listeriosis has been performed. Our cases of listeriosis showed a significant difference in this ratio and in the use of steroids relative to patients in the control group. Although steroid use increases neutrophil counts because neutrophil released from the pool of mature neutrophils in the bone marrow [22], the ratio of neutrophils to lymphocytes in our case group was lower than that in the control group. This result may assist in diagnosing listeriosis early.

A systematic review from researchers in China reported patients with nonperinatal listeriosis had a mortality rate of about 23.8% [23]. Their 30-day mortality rate of listeriosis was similar to that of non-listeriosis patients in our study (18.3% vs. 19.2%). Moreover, one living case developed a brain abscess. Clinician should consider listeriosis in patients with some risk factors even if the condition appears in a health care setting.

There are some limitations to this study. First, this study included only 11 cases of listeriosis and this limited report, arising from a single center, may have been unable to detect significant risk factors of listeriosis. Because the incidence of listeriosis in Asia is low as compared with that in Western countries,

large, multicenter studies should be conducted. Second, we could not comprehensively assess the presence or absence of central nerve infection in our study population because the analysis of cerebrospinal fluid was performed in only one case. In a previous study, the most common complication was neurolisteriosis [6]. As such, we might have underdiagnosed central nerve infections such as meningitis. Third, this study included only adult patients. Because neonatal cases were excluded, the results of this study cannot be extended to neonatal or pediatric patients. However, only one neonatal case over 10 years was identified. A future study focusing on the neonatal period is required.

Conclusions

This is the first case–control study of risk factors and outcomes in the comparison of listeriosis and non-listeriosis infection cases. Onset in the warm season, steroid use, and a lower ratio of neutrophils to lymphocytes were risk factors for listeriosis. These observations may help clinicians to detect listeriosis early on, especially in Asian populations where available recommendations are more limited. Additionally, because the 30-day mortality rate was high in both the listeriosis and non-listeriosis groups, clinicians need to take prompt action to identify the offending organism and establish a treatment plan.

Declarations

Ethics approval and consent to participate

This study was approved by the Tokyo Medical University institutional review board (approval no. T2020-0379). Written informed consent was obtained from all subjects for the publication of this report. A copy of the consent form is available for review upon request.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of the current study are available at the Tokyo Medical University Hospital.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

YW, IN and HW conceived and designed the study. YW and YM collected the data. YW analyzed the data and wrote the paper. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, table 1-2 is only available as a download in the Supplemental Files section.

Figures

Figure 1
Distribution of 11 admission months of *L. monocytogenes* bacteremia

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table.pdf](#)