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Infection caused by *Listeria Monocytogenes* in Bilbao, Spain: a 10-year experience (2010-2019)

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Abstract:
Listeriosis is a disease causes by the *Listeria monocytogenes* bacteria. The main agent of contagion is contaminated foods. Where immunocompetent patients are concerned, it may manifest itself as feverish gastroenteritis, while in immunosuppressed patients, much severe manifestations of the disease may occur: nervous system infections, endocarditis, and among pregnant women, spontaneous miscarriages or premature births.The aim of the present article is to carry out a descriptive, retrospective, epidemiological-clinical study, of all cases of listeriosis that have been diagnosed at University Hospital Basurto in the city of Bilbao between the years 2010 and 2019.

KEYWORDS

Listeriosis.
Infection.
Listeria monocytogenes.

Infección causada por *Listeria Monocytogenes* en Bilbao, España: un período de 10 años de experiencia (2010-2019)

Resumen:
La listeriosis es una enfermedad provocada por la bacteria *Listeria monocytogenes* que se contrae principalmente por la ingesta de alimentos contaminados. Se trata de un padecimiento que en pacientes inmunocompetentes suele comportarse como una gastroenteritis febril, mientras que individuos inmunosuprimidos pueden manifestar cuadros más severos como bacteriemia, infecciones de sistema nervioso central, endocarditis e inclusive abortos espontáneos o partos prematuros en embarazadas. El

PALABRAS CLAVE

Listeriosis.
Infección.
Listeria monocytogenes.

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objetivo del presente artículo es realizar un estudio clínico-epidemiológico descriptivo retrospectivo de todos los casos de listeriosis que se diagnosticaron en el Hospital Universitario de Basurto en la Villa de Bilbao (Vizcaya) entre los años 2010 y 2019.

GILTZA-HITZAK

Listeriosa.
Infekzioak.
Listeria monocytogenes.

***Listeria Monocytogenes*ek eragindako infekzioa Bilbao, Espainia: 10 urte. Esperientzia (2010-2019)**

Laburpena:
Listeriosia, orokorrean, jakien bitartez transmititzen den *Listeria monoctytogenes* bakterioak eragindako gaixotasun infekziosoa da. Gaixo immukonpetenteetan sukargastroenteritis antzerako sintomak sor ditzake, baina immunodeprimituetan bakteriemia, sistema nerbioso zentraleko infekzioak, endokarditisak, abortu espontaneoak edo erditze goiztiarrak eragin ditzake. Artikulu honen helburua 2010 eta 2019 artean Basurtuko Unibertsitate Ospitalean, Bilbon (Bizkaia), diagnostikaturiko kasuen azterlan kliniko-epidemiologiko deskriptibo erretrospektibo bat egitea da

Introduction

Listeria monocytogenes is an anaerobic grampositive bacillus, which behaves as an intra-cellular pathogen[1]. It is the causal agent of listeriosis, one of the most serious food transmitted illnesses known to man[2].

L. monocytogenes belongs to the Listeria gender, composed of 17 species among which the most relevant are: *L. monocytogenes*, *L. innocua*, *L. ivanovii*, *L.seeligeri*, *L.welshimeri*, and *L. marthii*[3]. Of the afore-mentioned, only 2 are pathogenic: *L. ivanovii* and *L. monocytogenes*, both of which affect rodents and humans alike[4, 5, 6].

L. monocytogenes was first described by Murray, *et. al* in 1926, while he was investigating an epidemic outbreak among laboratory animals. The first case of listeriosis ever reported on a human being took place 3 years afterwards, and the one responsible to do it was Nyfeldt[7]. It was not until the first decade of 1980, when this bacteria was confirmed to be a food-transmitted pathogen[8, 9].

Currently, 13 *L. monocytogenes* serotypes have been described, however, the ones responsible for the major part of infectious outbreaks are: 1/2a, 1/2b, and 4b[3]. This bacteria is widely distributed in Nature and can be isolated from diverse environments such as soil, water, vegetation, sewage systems, animal feed, farms, faeces both animal and human (it is calculated that up to 10% of the population is a stool carrier of *L. monocytogenes*), as well as animal feed processing-plants[3, 8, 9, 10].

Among the different sources from which the previously mentioned bacteria can be isolated, the most studied and relevant, are the animal feed processing-plants, these being responsible for most of the outbreaks[11].

Multiple outbreaks on an international range have been reported for the past several years, and have been confirmed to be related to a wide variety of foods: ice cream, ready-to-eat products, smoked fish, pâté, cheese, fruits and vegetables[12, 13].

The European Center for Prevention and Disease Control reported that between the years 2010 and 2015, 836 cases of listeriosis were confirmed only in Spain. However, this figure is difficult to confirm, since up to 2015 an *L. monocytogenes* infection was still not considered to belong to the list of diseases that compulsorily need to be declared by the General Direction of Public Health, part of Madrid´s Department of Public Health[14].

From the moment the Epidemiological Surveillance Web started its monitoring protocol for listeriosis, it was officially established that weekly reports with individualized data of both probable and confirmed cases of listeriosis, should be reported. On the other hand, any suspicion of an outbreak (2 or more cases of listeriosis keeping an epidemiological link between them), needs to be treated as an urgent notification[14].

Vizcaya's Epidemiological Surveillance Unit of the Basque Country declared 150 cases of listeriosis between the years 2010 and 2018. The mostly affected age group ranged between 70 and 74 years of age, with a rate of 6.96 cases per 100,000 inhabitants, and among the range group of 65 to 69 years, a rate of 4.52 cases per 100,000 inhabitants, were reported[15]. The autonomous communities that were primarily affected were: Basque Country, Cantabria, Rioja and Cataluña, while the Community of Valencia, Murcia and the Canary Islands, presented lower infection rates[16].

As far as the outbreak that occurred in Spain in 2019 goes, it triggered a profound interest among the medical community. Its source of infection was discovered in a lot of processed shredded meat[17].

The aim of the present study is to analyze the incidence and clinical-epidemiological features of L. monocytogenes infection in a third level hospital in Bilbao, Northern Spain, over a period of 10 years, from 2010 till 2019.

Methods

Within the trial study period, a systematic assessment of al listeriosis cases registered in the Clinical Documentation Service, took place at the University Hospital of Basurto, a public institution of third level located in Bilbao, Vizcaya, which handles a population of approximately 400,000 inhabitants.

The analysis consisted of the patients´ clinical histories who had been admitted from the 1st of January 2010 until the 30th of August 2019, following an item list drawn up by the authors and which included demographic variables related to symptomatology, diagnoses and treatment of *L. monocytogenes* infection.

Data analysis was obtained with the use of the statistical package SPSS version 22 IBM USA 2013.

The study took place after having strictly complying with the Bioethics Committee of the hospital, as well as the Helsinki Declaration. Patient anonymity was respected throughout the whole process, and information treated confidentially.

Results

28 cases for *L. monocytogenes* infection were detected. 5 of these needed to be excluded due to a lack of sufficient data in the file in order to be able to perform an appropriate analysis. The final sample was comprised of 23 cases, 12 men (52.2%) and 11 women (47.8%).

Two pediatric patients were detected among said population: a pre-term infant who became infected through vertical transmission, and a 2-year-old child.

The average age within the adult patients was: for men 66.9 +- 14.7 years, and for women 68.6 +- 13.3 years.

At the time of diagnosis, the majority of patients presented some type of co-morbidity, as shown in table I:

Table I
Comorbidities at time of diagnosis

Comorbidities	Frequency (Percentages)
Metabolic (diabetes mellitus)	3 (13%)
Oncologic	14 (60.9%)
Pregnancy	1 (4.3%)
None	5 (21.7%)

More than half of the patients who were studied had some type of neoplasm and at the time were undergoing chemo or radiotherapy, a fact that is consistent with listeriosis generally affecting immunosuppressed populations. Pregnancy was considered a comorbidity because of its immunosuppressant effects[17].

The table II shows the medical services where the diagnoses for listeriosis were established:

Table II
Listeriosis diagnosis by department

Department	Frequency
Internal Medicine	2 (8,7%)
Oncology	5 (21,7%)
Neurology	2 (8,7%)
Neonatology	2 (8,7%)
Pediatrics	1 (4,3%)
Hematology	1 (4,3%)
Emergency Room	9 (39,1%)
Rheumatology	1 (4,3%)
Gynecology	1 (4,3%)

The diagnosis was primarily established in the Emergency Room (39,1%). Such an outcome was made possible by the protocolled blood cultures sampling for patients with fever at the time of admission. Despite the fact that Basurto University Hospital has a department of Infectious Diseases, this is not a primary contact service.

The dominant symptom turned out to be acute fever of 37.9º C in 82,6% (19) of cases. Following diagnostic protocol, every patient with a fever must undergo a blood culture, which explains the fact that bacteremia was confirmed in 73,9% (17) of patients.

Listeriosis´ clinical picture is non-specific, therefore further symptomatology was evaluated: neurological abnormalities, respiratory failures, febrile seizures and diarrhea. In one case in particular, it was possible to isolate bacteria from an abscess developed after a prior surgical wound. In none of these cases a source of contagion was mentioned.

The most commonly used treatment was a combination of ampicillin and gentamicin, in 60,9 % (14) of the patients in the sample study. Continuing from a higher to a lower frequency: monotherapy with ampicillin 21.7% (5), penicillin 4.3% (1), ampicillin, gentamicin and corticosteroids 4.3% (1), levofloxacin and gentamicin 4.3% (1) and ampicillin, meropenem, linezolid and corticosteroids 4.3 % (1).

The average extent of the patients´ hospital stay was 20.3 days, while the average treatment duration was of 20.6 days.

Our study however, showed certain limitations. Firstly, it was a descriptive, retrospective study based in databases that are electronically kept within the computerized system of Osakidetza (Basque Health Services), and in paper. It was not a prospective surveillance analysis comprised of several entities. Furthermore, because of the fact that we were dealing with a low prevalence pathology, the size of our sample is small, therefore, the study´s results cannot be extended to the population as a whole.

Discussion

L. monocytogenes may contaminate a food processing plant through various routes, be it those related to the equipment used, the elements involved in food production or personnel changeover. Once inside the bloodstream, the bacteria may colonize and persist over a long period of time because it is comprised of several resistance mechanisms over elements, which have a negative impact on its survival[6, 10].

The most important pathway of contagion is through the intake of contaminated foods. 17. The physiopathology of *L. monocytogenes* infection is described in detail in the following chart[4, 8, 20, 21, 22].

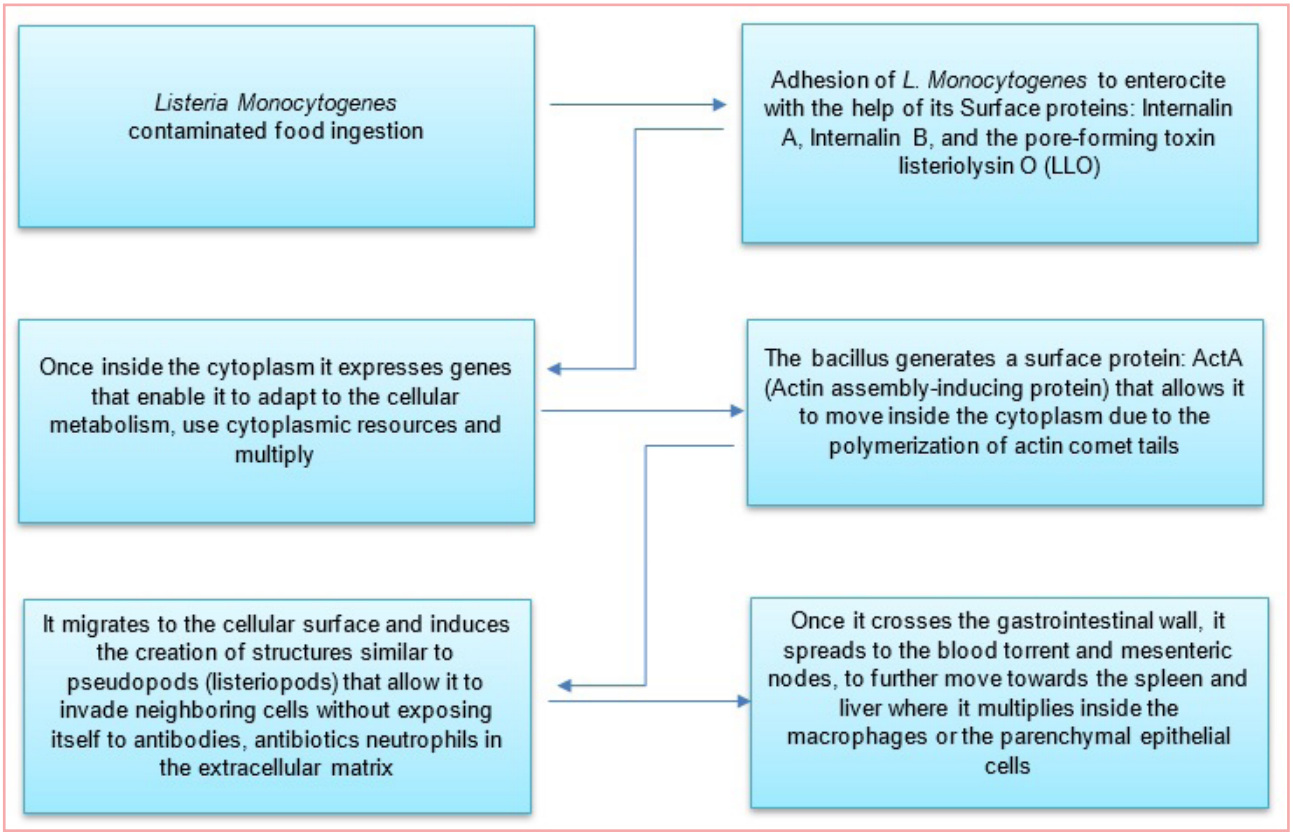

Figure 1. The physiopathology of *L. monocytogenes* infection.

This bacteria mostly affects immunosuppressed patients (infectious, neoplastic or metabolic causes), pregnant women, neonates and elders, while in healthy individuals *L. monocytogenes* may derive in a mild feverish gastroenteritis which in turn may cause diarrhea, myalgia and headaches[4, 12].

Among the previously mentioned population, this infection is dramatically more severe since it may manifest itself with bacteriemia, neumonia, encefalitis, endocarditis and sepsis[22].

Furthermore, because of its faculty to cross the blood-brain barrier (BBB), and the placental one, it is a common outcome among these patients to develop meningitis, meningo-encephalitis, brain abscesses, spontaneous miscarriages or premature births[11, 23]. In our case series a case of a pregnant woman was found. She came to the ER with fever and abdominal pain. The diagnosis of corioamnioitis was made and labor was induced at 35.5 weeks of gestation. It was a vaginal delivery with forceps. The newborn was treated during 21 days with ampicillin and gentamicin. At the moment he is 7 years old and sequelae free.

Therefore, it is possible to distinguish three forms of invasive listeriosis[23]:

1. Bacteriemia
2. Neurolisteriosis
3. Maternal and neonatal infection

As far as treatment goes, MONALISA study (a prospective, multicentric, observational study of cohorts published by The Lancet in 2017)[24] concluded that the optimal treatment for listeriosis relied in the prescription of amoxicilin. The mean for the extent of treatment varied according to the type of infection: 15 days for a maternal-neonatal infection,16 days for bacteriemia and 22 days for neuro-listeriosis.

Those patients who were prescribed a beta-lactam with anti-listeria coating, showed a threefold increase in survival rate in contrast with those patients who weren't prescribed this antibiotic. It is therefore a recommendation that treatment includes an aminoglucoside (gentamicin), due to the effect it has in the improvement of the survival rate[24].

The bacteria perishes quickly when exposed to heat. Consequently, it is eliminated with the application of

food-preservation mechanisms, such as pasteurization. Henceforth, the foods that are in a much higher risk of infection are: ready-to-eat foods or foods that are ingested raw[16].

Considering the above, the main measures that need to be taken in order to prevent listeriosis include: thoroughly cooking animal products, washing raw vegetables, avoiding non-pasteurized diary products, avoiding ready-to-eat foods, washing hands and kitchen appliances before their use and after manipulating raw vegetables.

Conclusions

Listeriosis is a disease that primarily affects immunosuppressed patients, independently of its cause.

In the face of an immunosuppressed patient with forthright clinical symptomatology of infection and a previous history of ingestion of a potentially contaminated food, the attending physician is required to exclude the diagnosis of *L. monocytogenes* infection.

In order to achieve this, he/she must obtain blood cultures and afterwards use all the necessary diagnostic tools available. By the same token, empiric antibiotherapy using the previously mentioned antibiotics is recommended (first-line penicillin and gentamicin) because of high survival rates presented at the early start of treatment [23, 24].

Authorship declaration

All the signing authors made substantial contributions to the conception and design of this study, as well as the acquisition and interpretation of data. The manuscript was prepared by Jasqui-Bucay Alan and Jasqui-Bucay Ariel and reviewed by the rest of the authors. The final version of the article was approved by all the authors.

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Interest conflict

None of the authors presents any conflict of interest.

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