

Epidemiology, clinical and imaging features of rhombencephalitis caused by *L. monocytogenes*. A retrospective observational study

Antonio J. Láinez-Ramos Bossini, Pablo Redruello-Guerrero, José P. Martínez-Barbero, Paula Gutiérrez-Jiménez, Carmen Gutiérrez-Jiménez, Mario Rivera-Izquierdo

Introduction. To date, few studies have explored the specific risk factors of patients with listeriosis who develop rhombencephalitis, and there is insufficient information regarding imaging findings and clinical symptoms in patients with this disease. This work aimed to analyze the imaging findings associated with *L. monocytogenes* rhombencephalitis in a cohort of patients with listeriosis.

Materials and methods. We conducted a retrospective observational study of all declared cases of listeriosis in a tertiary hospital from Granada, Spain, from 2008 to 2021. Risk factors, comorbidities, and clinical outcomes were collected for all patients. In addition, clinical symptoms and magnetic resonance imaging (MRI) findings were included for those patients who developed rhombencephalitis. Descriptive and bivariate analyses were performed using SPSS statistical software (IBM SPSS, version 21).

Results. Our cohort comprised 120 patients with listeriosis (41.7% women, mean age: 58.6 ± 23.8 years), of which 10 (8.3%) had rhombencephalitis. The most frequent MRI findings in patients with confirmed rhombencephalitis were T₂-FLAIR hyperintensity (100%), T₁ hypointensity (80%), scattered parenchymal enhancement (80%), and cranial nerve enhancement (70%), while the most frequent anatomical involvement were pons, medulla oblongata, and cerebellum. Complications occurred in 6 patients (abscess in 4, hemorrhage in 2, hydrocephalus in 1).

Conclusions. Rhombencephalitis is associated with an increased in-hospital mortality in patients with listeriosis. The anatomical distribution and imaging characteristics of neurolisteriosis could be useful to suggest the diagnosis. Future studies with greater sample size should explore the association between anatomical location, imaging patterns, and associated complications (e.g., hydrocephalus, hemorrhage), and clinical outcomes.

Key words. Central nervous system. *L. monocytogenes*. Magnetic resonance imaging. Prognosis. Radiology. Rhombencephalitis.

Introduction

Listeria, named after the pioneer of sterile surgery Sir Joseph Lister, is a genus of gram-positive rods. The morbidity and mortality associated to neurolisteriosis is very high [1], which justifies the need for a rapid diagnosis to allow appropriate antibiotic therapy (usually ampicillin or penicillin combined with gentamicin) to be administered.

Magnetic resonance imaging (MRI) offers high spatial and tissue resolution and is very useful to suggest the diagnosis of rhombencephalitis. However, no specific MRI protocols are available for suspected central nervous system neurolisteriosis, which may delay the definite diagnosis [2]. MRI signs of rhombencephalitis include as abnormally high signal intensity on T₂-weighted images, patho-

logic enhancement of the brain parenchyma or cerebrospinal fluid (CSF) spaces [3]. In addition, it is usually hypo to isointense on T₁-weighted images, and may show diffusion restriction. MR spectroscopy may be helpful in the differential diagnosis, as it may be useful in distinguishing an abscess from tumor. Remarkably, although listeriosis is the most common form of infectious rhombencephalitis, imaging findings remain nonspecific [4]. Although there are several works focused on describing the imaging findings typical of rhombencephalitis, studies correlating these imaging findings with other prognostic variables in patients with rhombencephalitis are scarce. Such associations could provide relevant information to shed light on the invasion process of *L. monocytogenes* into the brainstem, as pointed out by some authors [5].

Department of Radiology (A.J. Láinez-Ramos Bossini, P. Redruello-Guerrero, J.P. Martínez-Barbero). Department of Anesthesiology. Hospital Universitario Virgen de las Nieves (P. Gutiérrez-Jiménez). Instituto Biosanitario de Granada (A.J. Láinez-Ramos Bossini, P. Redruello-Guerrero, J.P. Martínez-Barbero, P. Gutiérrez-Jiménez, C. Gutiérrez-Jiménez, M. Rivera-Izquierdo). Department of Preventive Medicine and Public Health. Universidad de Granada (M. Rivera-Izquierdo). Service of Preventive Medicine and Public Health. Hospital Universitario Clínico San Cecilio. Granada, Spain (M. Rivera-Izquierdo).

Corresponding author:

Dr. Pablo Redruello-Guerrero. Instituto Biosanitario de Granada (ibs.GRANADA). Av. de Madrid, 15. E-18012 Granada.

E-mail:

pablorg239@correo.ugr.es

Acknowledgments:

The authors thank doctors Jorge Pastor, Francisco Romero, and Heriberto Busquier from the Neuroradiology Unit of the Hospital Universitario Virgen de las Nieves for their kind contribution in the analysis of MRI studies.

Accepted:

19.05.23.

Conflict of interests:

The authors declare no conflict of interest to disclose

How to cite this article:

Láinez-Ramos Bossini AJ, Redruello-Guerrero P, Martínez-Barbero JP, Gutiérrez-Jiménez P, Gutiérrez-Jiménez C, Rivera-Izquierdo M. Epidemiology, clinical and imaging features of rhombencephalitis caused by *L. monocytogenes*. A retrospective observational study. Rev Neurol 2023; 76: 385-90. doi: 10.33588/rn.7612.2023020.

Table I. General characteristics and risk factors stratified by the presence or absence of rhombencephalitis.

Variables	n (%) or Mean (SD)	Rhombencephalitis (n = 10)	No rhombencephalitis (n = 110)	p-value ^a
Sex				
Female	50 (41.7%)	4 (40%)	46 (41.8%)	0.911
Male	70 (58.3)	6 (60%)	64 (58.2%)	
Age	58.6 (23.8)	60.2 (16.2)	58.4 (24.5)	0.824
Outcome				
Survived	57 (47.5%)	5 (50%)	52 (47.3%)	0.869
Died during hospitalization	26 (21.7%)	4 (40%)	22 (20%)	0.142
Cause of death during hospitalization				
<i>Listeria</i>	23 (19.2%)	4 (40%)	19 (17.3%)	0.097
Cancer	2 (1.7%)	0 (0%)	2 (1.8%)	1
Infections	0 (0%)	0 (0%)	0 (0%)	–
Others	2 (1.7%)	0 (0%)	2 (1.8%)	1
Died during the first year of follow-up	18 (15%)	1 (10%)	17 (15.5%)	0.644
Cause of death during the first year of follow-up				
<i>Listeria</i>	0 (0%)	0 (0%)	0 (0%)	–
Cancer	9 (7.5%)	0 (0%)	9 (8.2%)	1
Infections	4 (3.3%)	1 (10%)	3 (2.7%)	0.297
Others	5 (4.2%)	0 (0%)	5 (4.5%)	1
Potential risk factors				
Diabetes Mellitus	32 (26.7%)	3 (30%)	29 (26.4%)	0.725
Cancer	33 (27.5)	3 (30%)	30 (27.3%)	1
Immunosuppression	20 (16.7%)	0 (0%)	20 (18.2%)	0.21
Cirrhosis	3 (2.5%)	0 (0%)	3 (2.7%)	1
HIV infection	3 (2.5%)	0 (0%)	3 (2.7%)	1
Pregnancy	8 (6.7%)	0 (0%)	8 (7.3%)	1
Alcoholism	7 (5.8%)	0 (0%)	7 (6.4%)	1
Absence of risk factors	13 (10.8%)	4 (40%)	9 (8.2%)	0.002

HIV: human immunodeficiency virus; SD: standard deviation. ^a p-value of Fisher's exact test or Kruskal-Wallis's test.

The aim of this work is to analyze the imaging findings in patients with a confirmed diagnosis of rhombencephalitis caused by *L. monocytogenes*.

Materials and methods

A retrospective hospital-based longitudinal observational study was designed. All cases of laboratory-confirmed listeriosis diagnosed at the Hospital Universitario Virgen de las Nieves, Spain. Data were accessed through the Andalusian Epidemiological Surveillance System. All cases of listeriosis reported between January 1st 2005 and December 31st 2021 were included in the study. Information was gathered on sociodemographic (i.e., sex and age), clinical presentation (including central nervous system involvement), and clinical outcome, including death at different time periods. In the particular case of rhombencephalitis, we collected variables regarding the presence of imaging abnormalities on emergency computed tomography (CT) and the main imaging findings observed on MRI, including the presence of T₂/FLAIR hyperintensity, parenchymal enhancement, abscesses, cranial nerve enhancement, obstructive hydrocephalus, and hemorrhage. Of note, all MRI studies were performed in 1.5 or 3.0 T machines with similar imaging protocols. Other variables were related to potential risk factors that could influence the outcome such as diabetes mellitus, hepatitis, cancer, cognitive impairment or states of immunosuppression, such as human immunodeficiency virus infection, autoimmune diseases, advanced age or pregnancy. The main outcome was the mortality rate, either during hospitalization or follow-up.

For the statistical analysis, absolute and relative frequencies were used to describe qualitative variables, while mean and standard deviation were used to express quantitative variables. Bivariate analyses including Fisher's exact and Kruskal-Wallis tests were used to study the association between qualitative and quantitative variables, respectively. All these analyses were carried out with SPSS statistical software (IBM SPSS, version 21).

This study was approved by the Provincial Ethics Committee of Granada (code: 2650-N-20). This study complies with the ethical standards stated in the Declaration of Helsinki.

Results

A total of 120 patients were included –51 women

(41.7%); mean age, 58.6 years (standard deviation: 23.8), range 0-98 years-. In the case of central nervous system involvement, meningitis (30.0%) and bacteremia (30.8%) were the most frequent clinical presentations. All 10 cases (8.3%) of rhombencephalitis were diagnosed based on MRI findings and confirmed by CSF analysis. Table I shows the main information regarding the variables analyzed in the entire cohort and it describes the comparative analyses between patients with rhombencephalitis and the rest of the cohort. A high percentage of patients with rhombencephalitis secondary to *Listeria* were found to have no risk factors (40%; $p < 0.05$).

Regarding clinical symptoms (Table II), all patients presented with refractory headache, which motivated performing an emergency brain CT. Cranial nerve symptoms were observed in 70% of patients, with a predominance of facial hypoesthesia (i.e., trigeminal nerve symptoms). Table II shows the imaging findings in the subgroup of patients with confirmed rhombencephalitis. All patients underwent emergency CT on presentation, but imaging abnormalities in the posterior fossa were observed only in 2 of them. Regarding MRI findings, all patients were found to have abnormally high T₂-FLAIR signal intensity, most patients showed T₁ hypointensity and scattered parenchymal enhancement in the affected areas. Of note, 5 patients had cranial nerve enhancement. One patient developed hydrocephalus during hospitalization, and 2 patients developed hemorrhage foci on imaging follow-up. Figures 1-3 depict illustrative examples of imaging findings in patients diagnosed with rhombencephalitis in our cohort.

Discussion

The frequency of rhombencephalitis in our cohort was 8.3%. Considering that the cohort included all cases of listeriosis (i.e., not only neurolisteriosis), this prevalence is similar to previous studies. For instance, Charlier et al [6] reported a series of 71 patients with microbiologically proven neurolisteriosis, of which 10% had imaging features consistent with rhombencephalitis. In addition, Beaumont-Vela et al [7] reported a series of 41 patients in an observation period of 15 years, and found that rhombencephalitis was present in 7.3% of cases. In Spain, Pelegrín et al [1] collected data on 59 patients with neurolisteriosis of whom 11 (18%) had rhombencephalitis. In our cohort, rhombencephalitis showed a weak association with premature mortality but, surprisingly, patients with no risk

Table II. Clinical symptoms and imaging findings in patients with rhombencephalitis.

Clinical symptoms	n (%)
Headache	10 (100)
Facial hypoesthesia	5 (50)
Nausea and vomits	4 (40)
Neck stiffness	3 (30)
Gait disturbance	2 (20)
Oculomotor symptoms	1 (10)
Dysphonia/dysphagia	1 (10)
Hemicorporal hypoesthesia	1 (10)
Imaging findings	
Suggestive findings on CT ^a	2 (20)
T ₁ hypointensity	8 (80)
T ₂ -FLAIR hyperintensity	10 (100)
Diffusion restriction	4 (40)
Scattered parenchymal enhancement	7 (70)
Ring-enhancing lesion (abscess)	4 ^b (40)
Cranial nerve enhancement ^c	5 (50)
Hydrocephalus ^d	1 (10)
Hemorrhage	2 (20)
Subdural enhancement	1 (10)
Anatomical location^e	
Midbrain	2 (20)
Pons	7 (70)
Medulla oblongata	9 (90)
Cerebellar peduncle ^f	5 (50)
Cerebellum	7 (70)

^a All patients underwent initial emergency brain computed tomography (CT). ^b The number of abscesses ranged from 1 to 4. ^c Trigeminal nerve was involved in all cases. One patient had concomitant hypoglossal nerve enhancement. ^d Hydrocephalus was diagnosed on CT. ^e Anatomical location of abnormal T₂-FLAIR signal hyperintensity. ^f The middle cerebellar peduncle was involved in four cases, and the inferior cerebellar peduncle in one case.

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Figure 1. Axial magnetic resonance images showing typical findings of rhombencephalitis in a 55 male patient presenting with headache, fever, gait disturbance and right facial hypoesthesia. Abnormal area of T₁ hypointensity (a), T₂ (b) and T₂-FLAIR (c) hyperintensity adjacent to the right anterior wall of the fourth ventricle, which is slightly compressed. Note the linear area of diffusion restriction (d and e) and enhancement (f) in the parenchymal trajectory of the right trigeminal nerve.

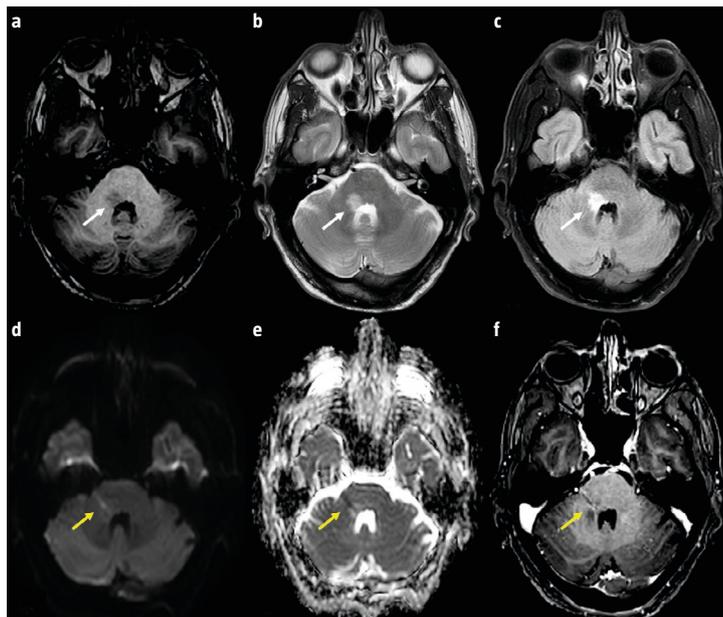
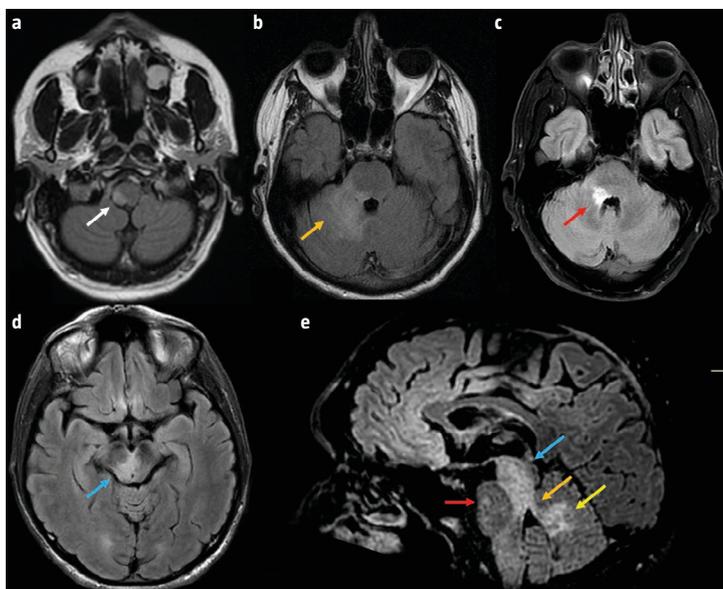


Figure 2. Patterns of posterior fossa involvement in different patients with confirmed rhombencephalitis from our cohort. Abnormal area of T₂-FLAIR hyperintensity involving the *medulla oblongata* (a), *brachium pontis* (b and e, orange arrows), pons (c, same patient as in figure 1; e, red arrows), and midbrain (d and e, blue arrows).

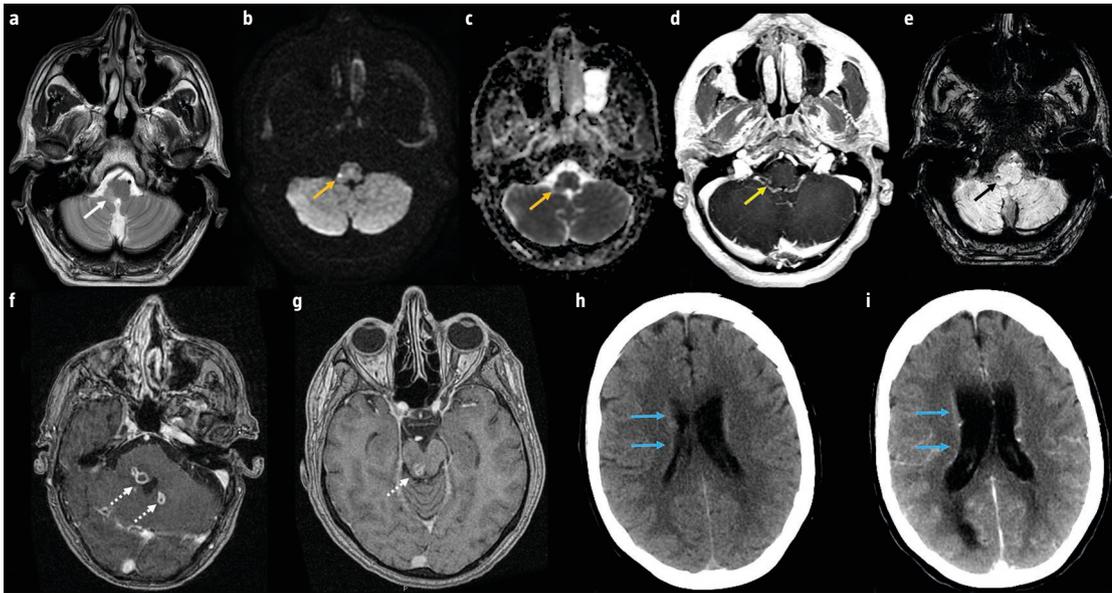


factors were found to have significantly higher mortality. In fact, previous studies of rhombencephalitis caused by *L. monocytogenes* were reported in previously healthy patients [8]. Based on these findings, we hypothesize that a strong immune reaction, which is more likely to occur in healthy patients, may play a significant role in prognosis. Therefore, the role of the immune system in rhombencephalitis should be addressed in future studies.

The clinical symptoms of rhombencephalitis secondary to *Listeria* infection (e.g., ataxia, hemiparesis or fever) and focal neurological signs related to cranial nerve involvement have also been used to define neuroinvasive listeriosis by some authors [9]. In our series, all patients presented headache and 40% had nausea and vomits, both of which are non-specific symptoms. Neck stiffness, gait disturbance, and symptoms related to cranial nerve involvement, all of which may be more suggestive of rhombencephalitis, were seen in a relatively low number of patients (10-30%).

Regarding imaging findings, T₁ hypointense and T₂ hyperintense areas due to increased water content at the site of infection were the most frequent radiological finding on MRI (Figs. 1 and 2; Table II), as in previous reports [10]. Diffusion-weighted images showing areas of increased diffusion restriction can be sometimes helpful, but their sensitivity is limited and largely depend on the kind of brain involvement (e.g., common in abscess). Of note, appropriate sequences (e.g., T₂* gradient-echo or susceptibility-weighted images) should be included in the exam to increase the sensitivity of hemorrhage detection, a potential although rare complication of rhombencephalitis. Gadolinium contrast agents administered intravenously can cross the blood-brain barrier if it has been damaged, enabling the detection of areas infected by *Listeria*, particularly abscess (i.e., ring-enhancing lesions) and cranial nerve enhancement. We observed that all patients with symptoms indicative of cranial nerve involvement (e.g., facial hypoesthesia, dysphagia) showed enhancement of the corresponding cranial nerve. A recent systematic review of rhombencephalitis caused by *L. monocytogenes* suggested that *Listeria* may invade the brainstem via the trigeminal nerve [5]. Therefore, clinical-radiological correlation regarding cranial nerve involvement could provide relevant diagnostic cues in patients with suspicion of *Listeria* rhombencephalitis, and potential imaging abnormalities of the cranial nerves most frequently involved should be carefully examined on contrast-enhanced MRI.

Figure 3. Illustrative examples of complications in patients with rhombencephalitis. Development of hemorrhage in a patient with medulla oblongata involvement. Note the abnormal area of T₂ hyperintensity (a, white arrow) with diffusion restriction (b and c, orange arrows) and nodular enhancement (d, yellow arrow). Follow-up imaging at 3 months shows a focal area of low signal intensity on susceptibility weighted image (e, black arrow), consistent with hemorrhage. Abscess formation denoted by ring-enhancement lesions involving the pons (f) and midbrain (g), dotted arrows. Hydrocephalus in a patient with rhombencephalitis. Note the increase in size of the supratentorial ventricular system at diagnosis (h) and on follow-up one week later (i).



The present study has several limitations. First, it was performed in one institution, which limits the generalizability of our results. Second, it is retrospective in nature, thus the actual prevalence of listeriosis might be underestimated, and neurological signs might not have been homogeneously explored. Finally, the low number of patients with rhombencephalitis precluded us from performing statistical analyses to explore the association of imaging findings and clinical outcomes. These limitations should be overcome in future studies, ideally prospective and multi-centric.

Conclusions

Listeriosis with central nervous system involvement is a potentially lethal disease with high morbidity and mortality. Rhombencephalitis secondary to *L. monocytogenes* characteristically shows brainstem involvement on MRI, and cranial nerve enhancement seems to be frequent and to correlate with clinical findings. Nevertheless, the high variability and non-specificity of clinical symptoms limit the early diagnosis of this condition. Consid-

ering the low number of previous studies addressing the specific manifestations of rhombencephalitis caused by *L. monocytogenes*, the role of imaging techniques in this context is still to be exploited. Further studies should explore the association between anatomical location, imaging patterns, and associated complications (e.g., hydrocephalus, hemorrhage), and clinical outcomes.

References

1. Pelegrín I, Moragas M, Suárez C, Ribera A, Verdaguer R, Martínez-Yelamos S, et al. *Listeria monocytogenes* meningoencephalitis in adults: analysis of factors related to unfavourable outcome. *Infection* 2014; 42: 817-27.
2. Zhao Y, Xu C, Tuo H, Liu Y, Wang J. Rhombencephalitis due to *Listeria monocytogenes* infection with GQ1b antibody positivity and multiple intracranial hemorrhage: a case report and literature review. *J Int Med Res* 2021; 49: 0300060521998568.
3. do Carmo RL, Alves-Simão AK, do Amaral LLE, Inada BSY, Silveira CF, Campos CMS, et al. Neuroimaging of emergent and reemerging infections. *Radiographics* 2019; 39: 1649-71.
4. Campos LG, Trindade RAR, Faistauer Â, Pérez JA, Vedolin LM, Duarte JÁ. Rhombencephalitis: pictorial essay. *Radiol Bras* 2016; 49: 329-36.
5. Karlsson WK, Harboe ZB, Roed C, Monrad JB, Lindelof M, Larsen VA, et al. Early trigeminal nerve involvement in *Listeria monocytogenes* rhombencephalitis: case series and systematic review. *J Neurol* 2017; 264: 1875-84.

6. Charlier C, Poirée S, Delavaud C, Khoury G, Richaud C, Leclercq A, et al. Imaging of human neurolisteriosis: a prospective study of 71 cases. *Clin Infect Dis* 2018; 67: 1419-26.
7. Beamonte-Vela BN, Garcia-Carretero R, Carrasco-Fernandez B, Gil-Romero Y, Perez-Pomata MT. *Listeria monocytogenes* infections: analysis of 41 patients. *Med Clin (Barc)* 2020; 155: 57-62.
8. Aymerich N, Lacruz F, Gállego J, Soriano G, Ayuso T, Villanueva JA. Rhombencephalitis caused by *Listeria*: clinical-radiological correlation. *An Sist Sanit Navar* 2004; 27: 245-8.
9. Moragas M, Martínez-Yélamos S, Majós C, Fernández-Viladrich P, Rubio F, Arbizu T. Rhombencephalitis: a series of 97 patients. *Medicine (Baltimore)* 2011; 90: 256-61.
10. Miranda-González G, Orellana PP, Dellien ZH, Switt RM. *Listeria monocytogenes* rhombencephalitis. Report of three cases. *Rev Med Chil* 2009; 137: 1602-6.

Epidemiología, clínica y resultados de imagen de rombencefalitis causada por *L. monocytogenes*. Un estudio observacional

Introducción. Hasta la fecha, pocos estudios han explorado los factores de riesgo específicos de los pacientes con listeriosis que desarrollan rombencefalitis, y no hay suficiente información sobre los hallazgos de imagen y los síntomas clínicos en pacientes con esta enfermedad. El objetivo de este trabajo fue analizar los hallazgos de imagen asociados a la rombencefalitis por *L. monocytogenes* en una cohorte de pacientes con listeriosis.

Materiales y métodos. Se realizó un estudio observacional retrospectivo de todos los casos declarados de listeriosis en un hospital terciario de Granada, España, desde 2008 hasta 2021. Se recogieron los factores de riesgo, las comorbilidades y los resultados clínicos de todos los pacientes. Además, se incluyeron los síntomas clínicos y los hallazgos de resonancia magnética (RM) de los pacientes que desarrollaron rombencefalitis. Se realizaron análisis descriptivos y bivariados utilizando el *software* estadístico SPSS (IBM SPSS, versión 21).

Resultados. Nuestra cohorte incluyó a 120 pacientes con listeriosis (41,7%, mujeres; edad media: 58,6 ± 23,8 años), de los cuales 10 (8,3%) tenían rombencefalitis. Los hallazgos más frecuentes en la RM de los pacientes con rombencefalitis confirmada fueron hiperintensidad en T₂-FLAIR (100%), hipointensidad en T₁ (80%), realce parenquimatoso disperso (80%) y realce de los nervios craneales (70%), mientras que la afectación anatómica más frecuente fue en la protuberancia, la médula oblongada y el cerebelo. Se produjeron complicaciones en seis pacientes (absceso en cuatro, hemorragia en dos e hidrocefalia en uno).

Conclusiones. La rombencefalitis se asocia a un aumento de la mortalidad intrahospitalaria en pacientes con listeriosis. La distribución anatómica y las características de imagen de la neurolisteriosis podrían ser útiles para sugerir el diagnóstico. Futuros estudios con mayor tamaño muestral deberían explorar la asociación entre la localización anatómica, los patrones de imagen y las complicaciones asociadas (por ejemplo, hidrocefalia y hemorragia), y los resultados clínicos.

Palabras clave. *L. monocytogenes*. Pronóstico. Radiología. Resonancia magnética. Rombencefalitis. Sistema nervioso central.