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CLINICAL AND RADIOLOGICAL PROFILE OF PATIENTS PRESENTING WITH NEUROLISTERIOSIS: A RETROSPECTIVE STUDY FROM A TERTIARY CARE HOSPITAL

Zainab Memon[1], Muhammad Abdullah[1], Fatima Mubarak[1]
[1.] *Aga Khan University Hospital, Karachi*

Corresponding author: ***Zainab Memon*** *Aga Khan University Hospital, Karachi* ***Email:*** *zainabmemon@live.com*

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ABSTRACT

Background and Objective

Neurolisteriosis, a central nervous system (CNS) infection caused by Listeria monocytogenes, is associated with significant morbidity and mortality, particularly in elderly and immunocompromised individuals. The objective of this study was to analyze the clinical and radiological data from the patients of this disease presenting to a tertiary care hospital.

Methods

This retrospective review analyzed clinical, laboratory, and neuroimaging data from 12 patients diagnosed with neurolisteriosis at Aga Khan University Hospital between September 2018 and March 2024. Diagnosis was confirmed through blood and/or cerebrospinal fluid cultures or polymerase chain reaction assays. Data was analyzed using Statistical Package for Social Sciences (version 25.0).

Results

The median age was 68.5 years, with 58.3% being elderly (>65 years) and 58.3% male. Most patients (91.7%) had underlying comorbidities, with diabetes mellitus and hypertension being the most common. Acute onset of symptoms was observed in two-thirds of cases. Fever (83.3%) and altered consciousness (75%) were the predominant presenting features. Meningeal enhancement was the most frequent neuroimaging finding (66.6%), followed by hydrocephalus (25%). The median time to radiological diagnosis (24 hours) was significantly shorter than to microbiological confirmation (72 hours). The mortality rate was 25%, with complicated clinical courses observed in 75% of patients.

Conclusion

Neurolisteriosis predominantly affects elderly and immunocompromised populations and presents with non-specific CNS infection symptoms. MRI plays a crucial role in early detection and management, given the delay in microbiological confirmation. Heightened clinical suspicion and prompt imaging can improve diagnosis and outcomes.

Keywords: Listeria monocytogenes, Central Nervous System Infections, Bacterial Meningitis, Neuroimaging

INTRODUCTION

Listeria monocytogenes, an intracellular gram-positive coccobacillus, is a relatively uncommon cause of infection with an incidence of less than 0.5 for every 100,000 individuals per year in both Europe and North America.[1–3] This infection commonly presents in extreme ages, pregnant women and the immunocompromised.[4] Despite its infrequency, it remains linked to considerable morbidity and mortality rates with minimal improvement in prognostic outcomes over the past decade, with significantly higher rates in those with a delay in diagnosis. Therefore, early identification and prompt treatment are vital in the improvement of the prognosis of the patient.[5,6]

L. monocytogenes has several clinical manifestations, the most common of them being self-limiting gastroenteritis in a healthy adult.[7] However, L. monocytogenes infection

often involves the central nervous system (CNS) as well, leading to a condition known as "neurolisteriosis".[1] This complication significantly escalates the mortality rate to between 17% and upwards of 30% among affected patients.[8] Moreover, this can be attributed to several significant factors, many of which work synergistically. These include an immunocompromised host typically coupled together with a delay in diagnosis which consequently, hinders appropriate initial treatment regimen.[9,10]

Several important mechanisms have been reported in literature that elucidate the pathogenesis of neurolisteriosis. It is established that L.monocytogenes either infiltrates the brain through hematogenous spread, leveraging its capability to traverse the blood-brain barrier or via neuron fibers connected to various peripheral tissues. Recently, utilizing a mouse model for neurolisteriosis, it was also observed that monocytes are required in order to access the CNS.[8,11]

Most commonly, L. monocytogenes invasion of the CNS causes meningitis or meningoencephalitis and less frequently, rhombencephalitis, ventriculitis and hydrocephalus.[12] In rare instances, L. monocytogenes can also manifest as intracranial hemorrhage and brain abscesses.[6,8]

Many of these manifestations, particularly Listeria Brainstem Encephalitis (LBE) progress swiftly and are fatal unless detected early with immediate treatment.[13] Despite the apparent urgency for many of these diseases, diagnosis continues to be a challenge due to a variety of reasons. The clinical presentation of neurolisteriosis is extremely diverse, and may resemble any other form of central nervous system infection.[14] Routine laboratory work-up is usually non-contributory.[13] The gold standard for diagnosing neurolisteriosis is the isolation of L. monocytogenes from either the cerebrospinal fluid (CSF) or the blood in the presence of relevant symptoms.[14] In cases where the serological testing turns out to be negative, clinicians rely more on findings of magnetic resonance imaging (MRI) brain as a supportive tool in the diagnosis of neurolisteriosis.[13,15]

Given the time-sensitive nature of many of these conditions, MRI is often regarded as one of the most effective diagnostic modality, for conditions such as rhombencephalitis and various other variants of L. monocytogenes CNS infections.[16,17] In spite of numerous advances in imaging techniques, there remains much paucity regarding the specificity of various findings to the wide variety of clinical manifestations of neurolisteriosis.[18] Lack of presence of characteristic findings in such cases results in a wide list of differentials. Radiological data was also analyzed from patients with CNS involvement from MONALISA, a national prospective cohort study involving patients of invasive listeriosis, in 2018 with an accumulation of 71 cases, and it was discovered that images were abnormal in 87% of cases. In spite of the high number of abnormal images, the authors concluded that neurolisteriosis presents as a range of neuroradiological images, none of which are distinctly specific but were found to be useful in determining the long-term prognosis of patients.[19]

We aim to present a series of diagnosed cases of neurolisteriosis, detailing their clinical progression and unique radiological observations. This, therefore, carries substantial significance owing to the paucity of literature concerning unique radiological findings, which serve as critical indicators for expediting diagnosis and directing subsequent interventions and treatment strategies.

METHODS

This was a retrospective study conducted at Aga Khan University Hospital. We reviewed retrospective data from 12 neurolisteriosis patients who presented patients between September 2018 to March 2024. Confirmation of diagnosis was made on the basis of isolation of listeria monocytogenes from blood cultures and/or cerebrospinal fluid cultures or biofire assay performed by polymerase chain reaction (PCR) technique. Clinical data including demographics, medical history and laboratory workup, along with radiographic findings were collected and analyzed. The study was approved by the institutional ethical review committee.

Data was analyzed using Statistical Package for Social Sciences (version 25.0). Descriptive statistics, such as frequencies, percentages and means were calculated. Additionally, correlation tests were performed between some factors and clinical or radiological outcomes.

RESULTS

The median age of our cohort was 68.5 years (range 0.25-85 years), with a significant majority (7; 58.3%) classified as elderly (>65 years). Notably, three patients (25%) were children or infants. Male patients constituted seven (58.3%) of the study group, while females accounted for five (41.7%).

Most patients (11 out of 12; 91.7%) presented with underlying medical conditions or comorbidities, primarily diabetes mellitus and hypertension, which coexisted in six patients. Among the pediatric cases, two were late preterm. Further information on comorbidities is provided in Table 1. The Charlson Comorbidity Index (CCI) was also calculated for these patients, with a median of 5.5 (range 0-9), indicating a significant risk of the predicted outcome resulting in death. Patients were further stratified according to their CCI scores: two patients (16.7%) had a low CCI score, while the remaining ten patients (83.3%) had a high CCI score.

Table 1: Distribution of comorbidities among patients of neurolisteriosis

Comorbid	**Number (n)**	**Percentage (%)**
Diabetes Mellitus	6	50
Hypertension	6	50
Multiple Myeloma	2	16.7
Chronic Liver Disease	2	16.7
Late Preterm	2	16.7
Other	3	25
Duration of Symptoms	**Number (n)**	**Percentage (%)**
Less than 3 days	5	41.7
More than 3 days but less than 7 days	3	25
More than 7 days but less than 14 days	2	16.7
More than 14 days	2	16.7

Additionally, over half of our patients (7; 58.3%) had an immunocompromised status, attributable to various causes. Two patients had undergone chemotherapy for multiple myeloma, while the rest were due to chronic medical conditions, such as autoimmune disease, malnutrition and chronic liver disease.

Two-thirds of our patient cohort had an acute presentation, with their symptoms lasting less than seven days. Only two patients sought medical care beyond 14 days of symptoms. More details are given in Table 1. Fever was the predominant symptom and presented in 10 out of the 12 (83.3%) patients. Interestingly, two of the three pediatric patients did not present with fever. Altered level of consciousness was the next most common symptom, observed in 75% of patients. A comprehensive breakdown of symptoms is provided in Table 2.

Table 2: Distribution of symptoms at presentation among patients of neurolisteriosis

Comorbid	Number (n)	Percentage (%)
Fever	10	83.3
Altered sense of consciousness	9	75
Seizures	2	16.7
Gait instability	2	16.7
Headache	2	16.7

Culture remained the gold standard for diagnosis, with most infections confirmed by both blood and cerebrospinal fluid (CSF) cultures (6; 50%). Four cases (33.3%) were diagnosed solely by blood culture, and two (16.7%) by CSF culture alone.

Radiographic findings from magnetic resonance imaging (MRI) were varied. Meningeal enhancement was the most frequent, observed in eight patients (66.6%), followed by hydrocephalus in four patients (25%), with one requiring external ventricular drain insertion. Further neuroimaging details are depicted in Figure 1.

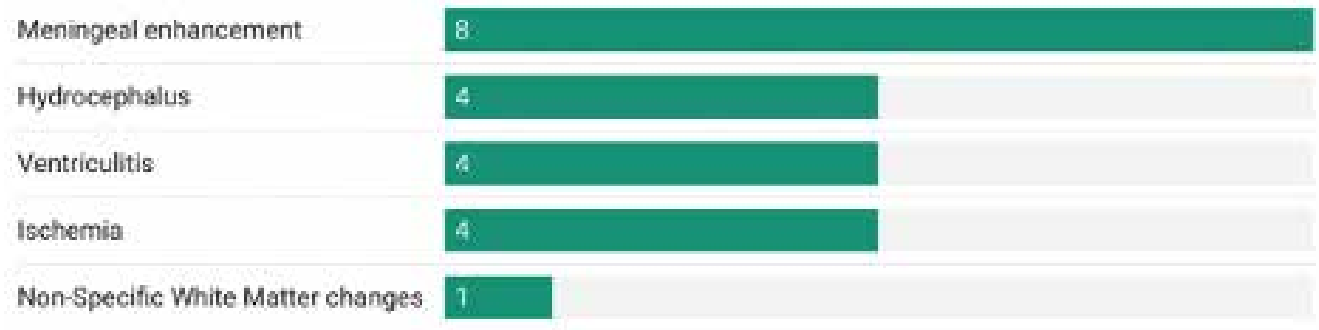

Figure 1: Radiological imaging findings amongst patients of neurolisteriosis

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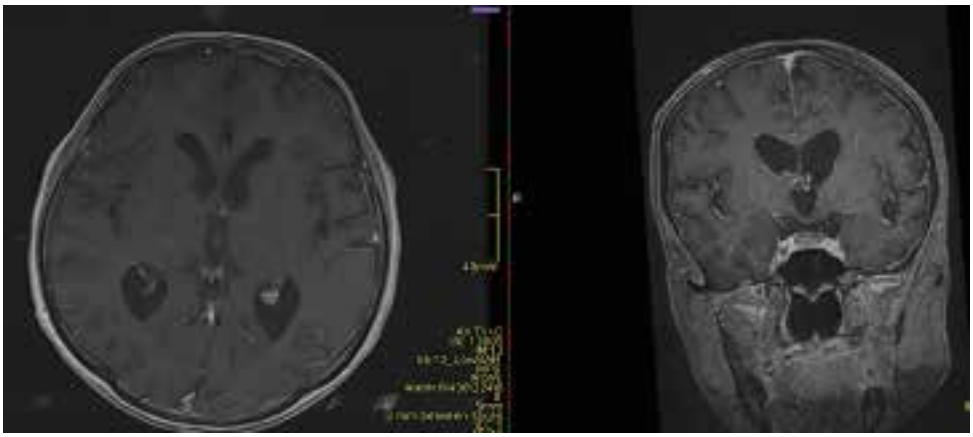
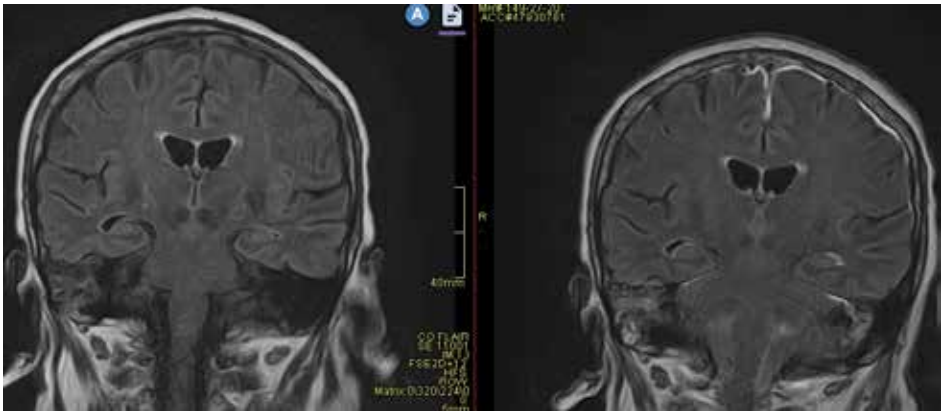
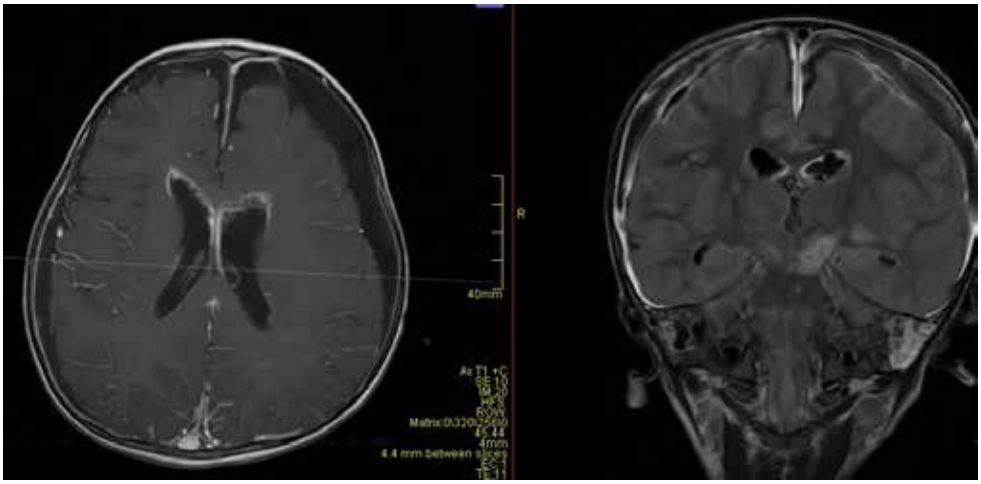


Enhancing parenchymal lesion in the left periventricular



Diffuse leptomeningeal enhancement.



Bilateral subdural collection, ventriculitis and encephalitis.

Figure 2: MRI findings in the patients

DISCUSSION

Listeria monocytogenes is a foodborne gram-positive bacillus known to cause febrile enteritis in immunocompetent hosts. However, it may also cause an invasive form of illness, which is more prevalent in immunocompromised individuals, elderly, pregnant women and newborns. Invasive listeriosis affecting the central nervous system has a mortality rate approaching 50 percent. About two-thirds of individuals who survive neurolisteriosis have residual neurological deficits, contributing to significant morbidity.[20] There are three major clinical variants of CNS listeriosis; meningitis/meningoencephalitis, rhombencephalitis and cerebritis with abscess formation. The three distinct forms of neurolisteriosis are distinguishable on the basis of pathogenesis and clinical course.

Irrespective of the anatomical targets of the disease, listeria mononcytogenes is known to affect the central nervous system via two proposed mechanisms. Hematogenous spread is more common in human hosts and is responsible for causing meningitis or meningoencephalitis through their interaction with blood-brain barriers. Cerebral abscesses are formed when L. monocytogenes gains access to the brain parenchyma traversing the cerebral capillary endothelium causing cerebritis. Listeria meningitis was the most common pattern of disease seen in our study population, consistent with previous literature. While rhombencephalitis, albeit rare, which is also associated with listeria monocytogenes, is thought to cause brainstem dysfunction via retrograde neuronal transport with a predisposition to affect cranial nerves. The mechanism of rhombencephalitis has been mainly derived from studies done in ruminants.[21]

With 58.3% of our patients being above 65, the median age of our cohort was 68.5 years, denoting the fact that neurolisteriosis mostly affects the elderly. This is consistent with the body of research indicating that older age is a major risk factor for listeriosis, and a predictor of mortality too. In accordance with a

data-based study done in Spain, immunosuppression, malignancy and chronic liver disease appear to be major comorbid conditions seen in association with neurolisteriosis.[23] While those who had no underlying medical illnesses exhibited better chances of survival. `In our study, we concluded that presence of multiple comorbid conditions, as quantified by high Charlson Comorbidity Index (CCI) score (found in 83.3% of our study population), was an independent predictor of worse outcomes, including severe neurological sequel and even death.

The clinical characteristics of neurolisteriosis are extremely diverse. Like other forms of bacterial infections of CNS, it may present with fever, headache, neck rigidity and/or alteration in the level of consciousness. However, seizures, cranial nerve palsies and other focal neurological deficits are not uncommon. The potential of rapid deterioration in neurolisteriosis is highlighted by the acute onset of symptoms in two-thirds of our group, indicating the need for immediate medical care. The most common symptom, seen in 83.3% of patients, was fever, which is a usual clinical presentation. Even in the lack of the typical signs of neurolisteriosis, physicians should nonetheless have a high index of suspicion due to the absence of fever in two pediatric instances in our study. Seventy-five percent of patients had altered consciousness at onset, which is a sign of serious neurological involvement in these circumstances.

Prompt diagnosis and treatment have paramount importance in improving long-term outcomes. Diagnosis is largely based on isolation of L. monocytogenes in blood or CSF culture. It is cumbersome to diagnose neurolisteriosis, owing to the variability associated with blood or CSF cultures.[22] In recent studies, it was established that listeria may be isolated in blood in about 60 percent of cases only, while cerebrospinal fluid is known to have much lower yield (up to about 40 percent). We concluded in our study that the maximum diagnostic yield is obtained when blood and cerebrospinal fluid (CSF) cultures are combined. In our population, the combined yield with blood and CSF culture was around 50% in comparison to blood culture (33.3%) and CSF culture (16.7%) alone.

On the other hand, the median time required for microbiological diagnosis (72 hours) was noticeably greater than the time required for imaging (24 hours). In a prospective study of 71 cases of human neurolisteriosis, it was found that diagnosis is often delayed until blood and cerebrospinal fluid cultures or polymerase chain reaction (PCR) results are available. The study noted that such diagnostic delays are common and can have a negative impact on clinical outcomes. This potentiates the need for developing more rapid diagnostic techniques. The role of magnetic resonance imaging in this regard is multidimensional.
MRI findings were varied in our patients, with meningeal enhancement being the most frequent abnormality.[23] The presence of hydrocephalus in 25% of cases, and the need for external ventricular drain insertion in one patient, highlight the potential for severe complications requiring surgical intervention. These findings emphasize the importance of early and thorough interpretation of neuroimaging in suspected cases of neurolisteriosis to identify and manage complications promptly. In the prospective study of 71 patients with neurolisteriosis, 83% had abnormal neuroimaging features. The findings on MRI ranged from various patterns of meningeal enhancement, enhancement of ventricular lining, cerebral edema and hydrocephalus to manifestations of parenchymal involvement in the form of ischemia, hemorrhages, abscess formation and non-specific white matter changes. Ventriculitis with hydrocephalus and parenchymal abnormalities were found to be associated with a poor three-month survival. This explains the fact that magnetic resonance imaging does not only help in defining the anatomical extent and severity of disease, but may also guide treatment response in patients and help physicians with predicting the clinical course and possible complications.

The mortality rate (25%) in our sample is in line with the significant death rates found in earlier research in neurolisteriosis. The two patients who left against their doctors' orders led to hindrance in the continuity of care. This highlights the need for better patient assistance and education. Diagnosis and management in the low middle income countries thus becomes cumbersome owing to various financial and geographical constraints.

The results of our study bring attention to the challenges in treating neurolisteriosis, especially in older and immunocompromised individuals. The high comorbidity rate in our cohort and the ensuing outcomes demonstrate the need for early intervention

and increased awareness in at-risk groups. To enhance patient outcomes, quicker diagnostic techniques (e.g. use of metagenomic next-generation sequencing of CSF) must be developed and put into use in response to the delays in microbiological diagnosis via conventional methods. Future studies should focus on determining the best management practices and investigating novel therapy modalities to lower the morbidity and mortality linked to neurolisteriosis.

CONCLUSION

Neurolisteriosis predominantly affects elderly and immunocompromised populations and presents with non-specific CNS infection symptoms. MRI plays a crucial role in early detection and management, given the delay in microbiological confirmation. Heightened clinical suspicion and prompt imaging can improve diagnosis and outcomes.

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Zainab Memon: Concept, Data analysis and interpretation, manuscript writing
Safia Awan: Data collection and analysis, manuscript writing
Ibrar Rafique; Data collection and analysis, Manuscript writing

All the authors have approved the final version to be published and agree to be accountable for all aspects of the work.