LISTERIA MONOCYTOGENES OUTBREAK – SERENDIPITY OR EMERGING THREAT?

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ABSTRACT

Background: *Listeria monocytogenes* is a facultative, catalase positive, anaerobic, gram-positive bacillus resulting in an infection known as listeriosis. It is one of the many neglected zoonotic diseases. Developing countries with low socio-economic status rely on animals especially cattle for their economy, have higher incidence rates of this disease. The infection spreads via bloodstream causing bacteremia and later may cause serious complications like meningitis. The disease is more common in immune compromised individuals including pregnant females, extremes of ages and those on chemotherapy, and steroids. Listeriosis is markedly under reported hence the true number of affected cases is not known.

Material and Methods: We are describing six cases of *Listeria monocytogenes* infection in a tertiary care hospital in Karachi, Pakistan. Blood cultures and body fluid sample - cerebrospinal fluid were collected from these patients and tested for infection.

Results: Out of these six cases, five patients had active bacteremia resulting in positive blood cultures. Two of these five patients had positive cerebrospinal fluid (CSF) for *Listeria monocytogenes* infection as well. One patient only had CSF polymerase chain reaction (PCR) positive without bacteremia.

Conclusions: Few cases of human *Listeria monocytogenes* infection are reported from Pakistan. In Aga khan University hospital, we identified six cases of *Listeria monocytogenes* infection in two weeks. We actively managed and studied the clinical course in affected patients. The risk factors were identified and patients were called for follow up. This study emphasizes on the development of prompt measures to prevent future incidences like these by identifying risk factors and disease process.

Keywords: *Listeria monocytogenes, L. Monocytogenes*, Listeriosis, Meningitis, Bacteremia, Zoonosis, Foodborne

BACKGROUND

Listeria monocytogenes (*L. monocytogenes*) is a gram positive, facultative anaerobic, intracellular bacillus that is transmitted through the consumption of contaminated food, hence the food-borne pathogen. In past the detection of this gram-positive rod was difficult but now with the emergence of new culture techniques and PCR based assays the process has become easy and reliable. The bacterium can survive in a wide temperature ranging from 1°C to 45°C. The incubation period is variable ranging from few days to months.

Incidence of listeriosis is more in people with compromised immune status including extremes of ages, pregnant women and patients taking chemotherapeutic drugs and steroids.[1] Pregnancy predisposes to this infection 18 times more as compared to the immune competent females and the underlying pathophysiology is still not clear. Disease prognosis is guarded in immune compromised patients having central nervous system involvement and in whom treatment is started late. Few cases are reported in immune competent adults and children.[2-5]

This bacterium can cross intestinal barrier, placenta and blood-brain barrier resulting in site specific infections including gastroenteritis, maternal-fetal infections and meningoencephalitis.[6-7] The infection usually starts with ingestion of infected/contaminant food product including raw or improperly cooked meat, eggs, dairy products, raw vegetables and fruits. The infection is almost always invasive resulting in bacteremia via gastro-intestinal tract and sometimes resulting in central nervous system complications including meningitis, meningoencephalitis and in rare incidences even abscess. The disease can also be transmitted to newborns via placenta.

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It is mainly a zoonotic agent but sporadic human cases are also reported and worldwide outbreaks are reported.[8] Most outbreaks were food borne involving dairy products mostly cheese, unpasteurized milk and milk products, raw meat, salads, canned, frozen and prepackaged food products.

The incidence of listeriosis is declining due to early detection of infection, availability of antibiotics, development of preventive strategies like pasteurization. The disease incidence in immune-competent patients is rare and few case reports and series are present in literature. In our study we enrolled all patients who had listeriosis in a specific time period of two weeks. All patients were hospitalized and disease process was monitored. Antibiotics were given according to culture and sensitivity report and all patients were discharged in stable condition.

MATERIAL AND METHODS

This study reports six cases from a single clinical setup - Aga Khan University Hospital (AKUH), which is a quaternary care hospital in Karachi, Pakistan. Data was collected over a period of two weeks. Medical records of the patients were collected from HIMS-Health Information Management System department and microbiology laboratory department AKUH. HIMS is an integrated, specialized institution-based information center in AKUH. Study was approved from Human Ethics Review Committee, Aga Khan Hospital Karachi (2019-1976-5076).

Diagnosis was confirmed in all cases by either positive blood cultures or CSF PCR or both. Blood cultures were performed in all cases. Lumbar puncture was performed and CSF was sent for PCR - BioFire-film array meningitis/encephalitis panel (by BioFire Diagnostics LLC, Salt Lake City Utah) in patients with signs and symptoms of meningo-encephalitis. Radiology test - MRI (magnetic resonance imaging) brain was performed in five patients.

RESULTS

We are describing six cases of listeriosis recently diagnosed in an adult population. Of these six cases, five presented during course of just 14 days. Microbiological tests were performed in all patients. Five patients had active bacteremia with positive blood cultures and two patients also had concomitant positive CSF for *L. monocytogenes*. One patient only had CSF PCR positive without bacteremia. Culture and sensitivity were performed in all cases. All strains of *L. monocytogenes* either in blood or CSF had same sensitivity pattern showing susceptibility to ampicillin, trimethoprim/sulfamethoxazole, and meropenem. Radiological test – MRI brain was performed in patients (A, B, C, D and F) with altered sensorium and also in those in patients with high suspicion of central nervous system involvement. Brain MRI scans of cases A, B, C, D and F are shown with findings in Figure-1, 2, 3,4 and 5 respectively.

All patients were started on appropriate therapy as per culture and sensitivity report within 72 hours of diagnosis. Patients were given combination therapy with Ampicillin 2gm every 6 hourly in case of bacteremia and every 4 hourly in case of meningitis along with gentamycin 1.7mg per kg per dose. All these patients were from distinct and discrete geographical areas and no commonalities were found. All six patients were discharged in stable condition. Clinical demographic information and course of all these patients is mentioned in Table-1.

Table-1: Clinical features and outcomes of patients with listeriosis.

CASE	Age/ gender/ Residence	Co morbids	Risk factors	Clinical manife-stations	IF markers and WBC	MRI brain	Sample sent	Empiric treatment	Directed therapy	ICU	Length of stay (days)	Outcome
A	45/M KHI-PAK	HCV CLD	-	Fever + ASOC	Neg WBCs-raised	+ve	Blood + CSF **(BFM)**	CTX + ACY + VANC	AMP+ GENT	Yes	16	discharged
B	66/F Dubai	DM, CKD, HTN	-	Fever	Raised WBCs-raised	+ve	Blood	CTX	AMP+ GENT	-	34	discharged
C	68/F (Interior Sindh)	DM, TB	Cattle at home	Fever + ASOC	Neg WBCs-raised	+ve	Blood + CSF **(BFM)**	CTX + ACY + VANC	AMP+ GENT	-	7	discharged
D	52/F	DM	-	Fever +	Raised	+ve	CSF	CTX +	AMP+	-	9	discharged

	(Interior Sindh)			ASOC	WBCs-raised		**(BFM)**	ACY	GENT			
E	77/ F Khi-Pak	DM	-	Fever	Raised WBCs-raised	NA	Blood	Pip/tazo	AMP+ GENT	-	8	discharged
F	82/ F Khi-Pak	AIHA, HTN, Hypo-thyroid	-	Fever + ASOC	Raised WBCs-raised	+ve	Blood	CTX + ACY + VANC	AMP+ GENT	-	12	discharged

Table-2: Clinical features and outcomes of patients with listeriosis prior to 2019.

Past cases												
G	35/F (Aug 2012) Khi-Pak	Post TB bronchi ectasis	Steroids	Fever + ASOC + Headache	NA WBCs -raised	NA/ CT brain Neg	Blood + CSF CS	CTX+ ACY + VANC	AMP+GENT	-	13	Improved and discharged
H	76/F (Mar 2014) Khi-Pak	DM, AIHA, CKD, IHD	Steroids	Fever + ASOC + GTC	Raised WBCs -raised	NA/ CT brain +ve	Blood + CSF CS	CTX+ ACY + VANC	AMP+GENT	Yes	3	Expired
I	69/F (May 2017) Khi-Pak	NHL	Chemo-therapy	Fever + ASOC + PR bleed	NA WBCs -low	Done but Neg	Blood + CSF CS	CTX + Pip/tazo	AMP+GENT For first 3 days then MERO + GENT	Yes	15	Expired

IF-inflammatory markers, MRI-magnetic resonance imaging, ICU-intensive care unit, F-female, M-male, KHI-PAK-Karachi-Pakistan, HTN-hypertension, DM-diabetes mellitus, CKD-chronic kidney disease, TB-tuberculosis, AIHA-autoimmune hemolytic anemia, IHD-ischemic heart disease, NHL- non Hodgkin's lymphoma, ASOC-altered state of consciousness, GTC-generalized tonic clonic seizures, PR-per rectal, WBC-white blood cells/leucocyte count, CT-computed tomography, CSF-cerebrospinal fluid, BFM-BioFire meningoencephalitis panel, CTX-ceftriaxone, ACY-acyclovir, VANC-vancomycin, pip/tazo-piperacillin/tazobactem, AMP-ampicillin, GENT-gentamycin, MERO-meropenem

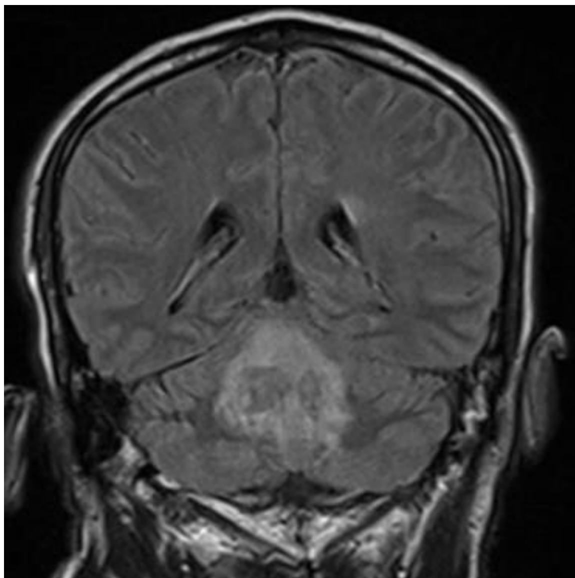

Figure-1: Showing an ill-defined abnormal signal intensity area identified in the cerebellar vermis, it is appearing heterogeneously hyperintense.

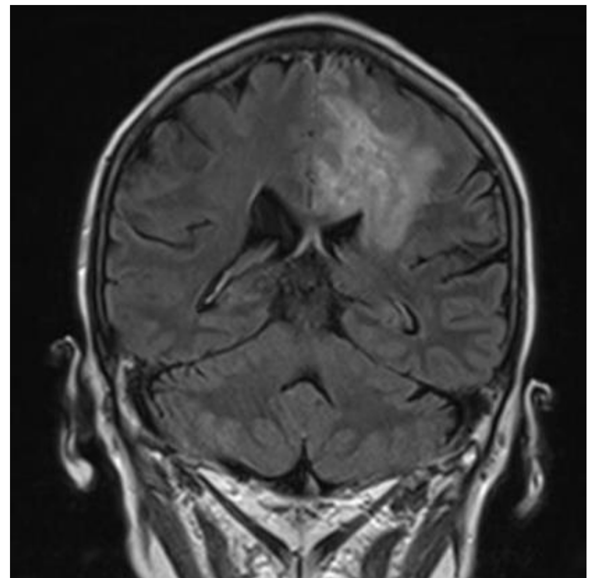

Figure-2: Showing focal sub-acute infarction in the left periventricular region extending into the posterior limb of left internal capsule and an ill-defined abnormal signal intensity area in the cerebellar vermis with extension of abnormal signals into the brainstem.

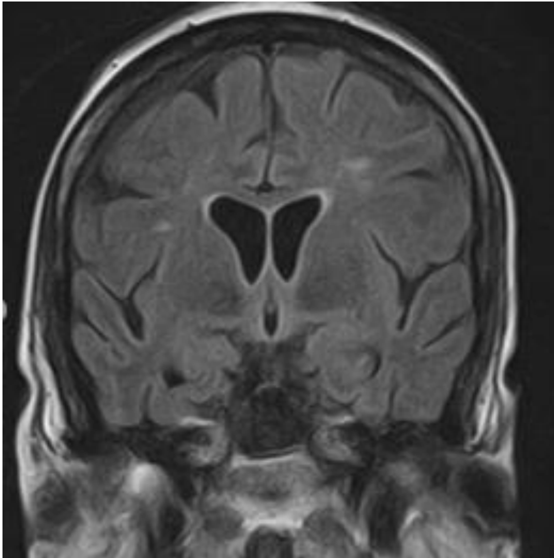

Figure-3: Showing hyperintense foci noted in periventricular and deep white matter bilaterally.

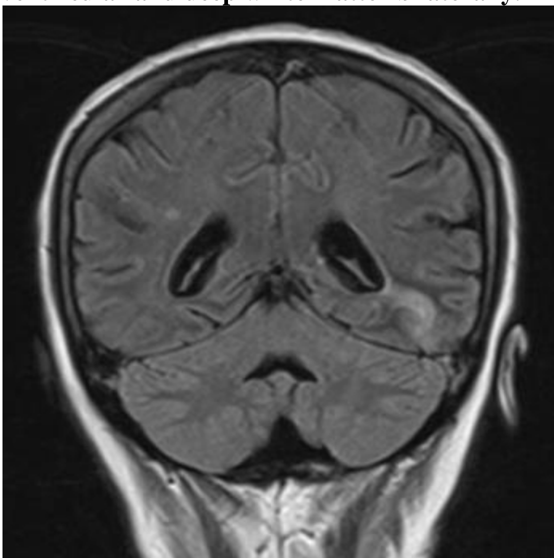

Figure-4: Hyperintense abnormality is identified involving the left occipito-temporal gyrus.

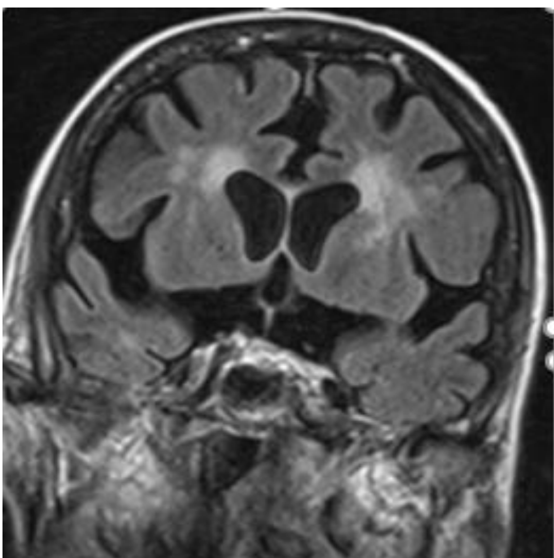

Figure-5: Hyperintensities are identified in the periventricular and subcortical location.

DISCUSSION

L. monocytogenes is a ubiquitous environmental organism. This organism is pathogenic to both animals and human population. Many strains are present but most of the literature focuses on the virulence and pathogenicity of *L. monocytogenes.* This bacterium is rather a sensitive strain and is usually susceptible to all first line agents including penicillin (ampicillin), carbapenem (meropenem), aminoglycoside (gentamycin) and sulfa drugs (cotrimoxazole) but with emerging use of antibiotics, resistance strains are also emerging. Currently 21 species are identified in the environment including *L. monocytogenes* and using advanced genetics like whole genome sequencing the phenotypic and genotypic correlation is made with already existing strains.[9]

Listeriosis, a disease caused by *L. monocytogenes* is rather an important yet curable foodborne infection. The prognosis of this disease depends on many factors but the most important is the underlying immune status of a patient. The disease is almost always invasive and the bacteremia result in further complications.[10] The virulence of the bacterium also lies in the fact that it is an intracellular pathogen and this fact should be kept in mind while using antibiotics thus only antibiotics are used that have good or sufficient cellular penetration ability. Mostly the disease is known to occur secondary to the consumption of dairy products but due to the introduction of pasteurization techniques the incidence is rather low. However, usage of cheese and ice-creams are still important agents that spread the bacterium and even result in outbreaks. The organism has the ability to survive in biofilms and develop resistance to surface sanitizers thus resulting in prolonged survival in food items like fruits and vegetables. Consumption of raw vegetables and fruits either directly or in the form of salads, contaminated with *L. monocytogenes*, result in point outbreaks in community.[11] Many outbreaks are being reported on the official site of Communicable Disease Centre secondary to consumption of fruits, vegetables and salads. There is ample evidence of its presence in dairy milk and poultry in Pakistan.[12,13]

Human infection outbreaks have rarely been reported in past in Pakistan.[14] Most outbreaks reported in literature are in animals. In our study we managed to collect data of patients presented in a single clinical set up in a specific time period that was after Eid. Pakistan is a Muslim country and every year the Muslim festival

of Eid-ul-Azha, creates an opportunity of sustained close interactions between large and small ruminants and humans over a period of days to weeks. Cattle is transported from rural areas of the country to the cities for sacrifice, which takes place in houses and on streets. The event has previously been associated with outbreaks of Crimean Congo Hemorrhagic fever in Pakistan.[15] However, in 2019 during Eid-ul-Azha, the province of Sindh recorded the highest rainfall in august with extensive flooding, loss of life and damage to civic amenities.[16, 17] This natural catastrophe resulted in poor sanitary measures and it was right after these events; we observed a surge in *L. monocytogenes* cases. Keeping in mind that all patients belong to different areas of Sindh and had different co-morbids but same religion and religious practices (they all conducted sacrificial ceremony in their homes); these two factors were assumed to be related to this event.

It can be expected that such coincidence of heavy rainfall with Eid-ul-Azha in the future, may lead to similar surge in listeria cases. The unusual surge in cases of Listeria can probably be attributed to interplay of climatic factors, the burden of Listeria in the environment and the opportunity for the organism for close interaction with humans.

Global distribution and trends of *L. monocytogenes* infection were recently reported in an article showing 123 *L. monocytogenes* events from 1996 through 2018. 65% were associated with outbreak events, 11% were associated with sporadic cases, and 24% were not associated with human cases. *L. monocytogenes* contaminated food articles were identified in all precautionary recall events.[18] The need of the time is to identify the risk factors of listeriosis resulting in such outbreaks and devise counter attack measures.

CONCLUSION

This study emphasizes on increasing number of listeriosis cases in a fixed time period of two weeks. The study deals with clinical course of admitted patients and probable underlying risk factors. Identification of all patients in a specific time period, points towards the need to device a system that ensures early identification of source and warrants provision of safe and hygienic food products and distribution. The disease is easily preventable. The need is to spread awareness regarding the mechanism of transmission. Educating masses especially the one in food industry regarding safe handling of food products and cleansing mechanism for raw food material especially fruits and vegetables is very important. Thus, focusing our efforts in identifying the risk factors and combating them will result in prevention of listeriosis and ultimately lower the incidence of outbreaks. Improved and rapid diagnostics also play an important role in clinical course of disease. The key is to lower the incidence of listeriosis which will ultimately lower the morbidity as well as mortality.

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