Invasive Listeriosis: Molecular Determinants of Virulence and Antimicrobial Resistance

Sir,

Human listeriosis causes severe disease and, when invasive, leads to high fatality rates. Clinical spectrum is varied with septicemia being more common, followed by meningoencephalitis in immunocompromised individuals and elderly.[1-3] *Listeria monocytogenes (Lm)* has a higher misdiagnosis rate with fast progression and poor prognosis.[4,5] Conventional culture method using blood or cerebrospinal fluid is time-consuming and has very low positive detection rate.[6] Despite adequate antibiotic treatment, the overall mortality is still high (25%–30%)

Table 1: Clinical and microbiological characteristics of listeria isolates

ID	Clinical syndrome	Risk factors	Patient outcome	Penicillin (μg/ml)	TMP/SMX (μg/ml)	oatA	PBP3	Acquired genes	Efflux genes
A	Lower respiratory tract infection	Posttuberculosis sequelae	Lost to follow-up	0.75	0.064	S96A, D440E, After 433 DK insertion, After 442 DSKE insertion, A443T, S445A, S449N, E450G, K452N, E453Q, K456V, S463T, I470M, D539E, A576S, and A607S	G66S, N98D, D171E, A223D, P236A, T580A, K584A, E608Q, and I650V. fosX, mbl	fosX, mbl	mepA, msrA, norB
B	Meningo-encephalitis	Type 2 diabetes mellitus Systemic hypertension Chronic kidney disease stage 5	Recovered	0.75	0.064	-	-	fosX, mbl	mepA, msrA, norB, mdrT (lmo2588)
C	Septicaemia	Malignancy	Expired	0.25	0.064			fosX, mbl	mepA, msrA, norB, mdrT (lmo2588)

PBP3: Penicillin-binding protein 3, TMP/SMX: Trimethoprim/Sulphamethoxazole

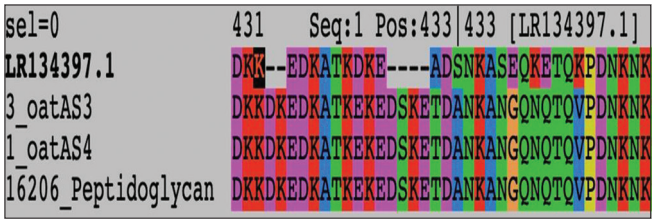

Figure 1: Protein multialignment showing insertions and mutations in *oatA* gene

and neurological sequelae are frequent. In this short report, we describe three clinical cases of *Lm* identified using conventional method; subsequently, the strains were characterized using next-generation sequencing. The clinical and microbiological characteristics of the isolates of the three patients are summarized in Table 1. All the three patients had risk factors such as type 2 diabetes mellitus, systemic hypertension, chronic kidney disease stage 5, lung fibrosis, and malignancy (germ cell tumor), which leads to impaired cell-mediated immunity, further predisposing to severe infection. ResFinder revealed only *fosX* gene in all three genomes. Accordingly, the study isolates were resistant to cephalosporins and susceptible to ampicillin, penicillin, and SXT (Trimethoprim/Sulphamethoxazole). Very few compounds have a bactericidal effect on *Lm* cells. Ampicillin or penicillin G was reported to be the best treatment options for listeriosis based on their bacteriostatic effect. The combination of AMP/PEN in combination with gentamicin will enhance the bactericidal effect of the therapy.[7]

Intrinsic resistance to cephalosporins was reported to be mediated by *oatA* mutations and PBP3 mutations. In the study isolates, the site of insertions and non-sense mutation in *oatA* were in S96A, D440E, after 433 DK insertion, after 442 DSKE insertion, A443T, S445A, S449N, E450G, K452N, E453Q, K456V, S463T, I470M, D539E, A576S, and A607S. Regions of mutations in PBP3 were G66S, N98D, D171E, A223D, P236A, T580A, K584A, E608Q, and I650V [Figure 1]. *OatA* mutants were known to induce early secretion of proinflammatory cytokines and chemokines *in vivo*, which recites the importance of *oatA* in limiting innate immune responses, thereby promoting bacterial survival in the host.[8] This insertional inactivation of *lmo0441* and *lmo2229* (coding PBP3 and PBPA2, respectively) greatly reduces the intrinsic resistance of *Lm* to cephalosporins.[9] The patient B, who had a favorable outcome, was initiated on ampicillin with gentamicin following the culture reports, hence showed clinical recovery. The patient C was initiated on carbapenem, which did not modify the disease course and led to adverse outcomes. In this study, insertions and mutations reported in *oatA* and PBP3 gene were known to be the primary mechanism of resistance to higher generation cephalosporins. This study adds to the existing evidence on the resistance mechanisms of Lm and emphasises the importance of microbiological diagnosis, and also indicates the significance of considering the host predisposition before initiating empirical therapy with higher antibiotics such as cephalosporins or carbapenems.

Research quality and ethics statement

The authors followed applicable EQUATOR Network (https://www.equator-network.org/) guidelines, notably the CARE guideline, during the conduct of this report.

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Conflicts of interest

There are no conflicts of interest.

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