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LISTERIOUS INVASION OF THE CENTRAL NERVOUS SYSTEM

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As described by Drevets et al. [1] cases of human meningitis caused by gram-positive diphtheroid bacilli later thought to be Listeria monocytogenes were identified in 1915 by Atkinson [2] and in 1918 by Dumont [3]. A clear association between L.monocytogenes and CNS infection in humans was proven in 1945 by Kaplan [4], who found that meningitis was present in 22 of the first 36 published case reports. Latest data suggest that CNS infection is present during invasive listeriosis in (28-79)% of cases in nonpregnant adults and in (13-44) % of neonates [1]. 22% of pregnancy-related cases resulted in fetal loss or neonatal death [5]. According to published annual dates concerning food-related illness and death in the United States L.monocytogenes is responsible for less than 0.1% of morbidity but supports 27.6% of mortality [1].

CNS infection with L.monocytogenes can manifest with different signs of meningitis, meningoencephalitis or encephalitis. The most common symptoms are headache, fever and altered sensorium including confusion, lethargy, and coma. Seizures and focal neurological findings including cranial nerve palsies or polyradiculoneuritis are also observed [5, 6]. In cases of brainstem encephalitis disphagia and cranial nerves lesion are often the first clinical signs [5]. CSF abnormalities can manifest with either a polymorphonuclear or a mononuclear predominance but are reported to show lower total leukocyte and protein concentrations compared with meningitis caused by extracellular bacterial pathogens [5]. Presence of bacteria in CSF is also uncommon [1, 5, 6].

Postmortem pathological findings in the brain are highly diverse and can include purulent meningitis, meningoencephalitis, microabscesses, focal hemorrhages and areas of necrosis [1, 5]. Histological analysis commonly shows vasculitis with perivascular lymphocytic cuffing and mononuclear cell infiltration of the vessel walls. Bacilli are present in the necrotic parenchymal lesions but are not typically found in the perivascular cuffs. Pus in the abscesses contained both intracellular and extracellular bacteria [1, 5, 7]. As generally accepted, the diversity of clinical and pathological signs reflects mainly the diversity of causative agent abilities to CNS entry.

The etiological agent of listeriosis is Gram-positive, rod shaped, motile, non-spore forming bacterium Listeria monocytogenes that has aerobic and facultatively anaerobic characteristics. It grows best at neutral to slightly alkaline pH, is capable of growth at a wide range of temperatures (from 1 to 45°C) and well resists temperatures under 0°C. L.monocytogenes usually contaminates food of animal origin (more frequent it is milk and fermented milk products), fishery products, or raw vegetables [1, 7].

It is known at least 13 serotypes, three of which (4b, 1/2b, and 1/2a) cause 90% of all human listeriosis. The single recognized virulence factor is listeriolysin O (LLO), a hemolytic extracellular protein. Failure to produce LLO renders a strain avirulent when tested in the mouse model [7].

L.monocytogenes is successful intracellular pathogen, which can infect different cell types and spread from cell to cell without leaving the intracellular compartment. In consequence of this lifestyle L.monocytogenes-specific CD8+Tcells are crucial for bacteria clearance.

Intracellular life cycle consists of internalization by professional phagocytes or other cells, escape from the phagosome, cytoplasmic multiplication, intracellular mobility by means of bacteria-induced host actin polymerization, and cell-to-cell spread. Phagocytes internalize bacteria through a variety of opsonin-dependent and opsonin-independent mechanisms. Entry into other cells L. monocytogenes can induce by using its own invasion proteins such as internalins (Inl A, Inl B). In murine macrophages and in cell lines derived from these cells, escape of L.monocytogenes from the phagosome is absolutely dependent on LLO and is facilitated by a secreted phosphatidylinositol-specific phospholipase C [8].

Penetration of L.monocytogenes into the host organism commonly takes place through intestinal epithelium overlying Payer's patches. Subsequent transport to the mesenteric lymph nodes, spleen and liver, which is a major site of infection, as well as other sites of system dissemination including CNS, most probably is supported by cells of the monocytic/macrophage lineage. Cell-sorting experiments early after infection revealed that CD8a+DCs are the first target population in the spleen, before other cell types become infected [9]. It can be proposed that to the central nerve system L. monocytogenes has been carried by peripheral blood monocytes or definite subpopulation of monocyte derived cells as far as this cells are able to permeate blood-brain barrier under physiological conditions and acquire markers which is peculiar to microglia [10].

Elegant study on this topic has been performed by Join-Lambert O.F. et al. [11] in experimental model of acute listeriosis in the mouse. It was shown that bone marrow is previously unrecognized reservoir of L. monocytogenes-infected myeloid cells, which can play a crucial role in the pathophysiology of central nervous system invasion. It was determined, that at the early phase of infection bacteria invade and rapidly grow in bone marrow cells identified as bone marrow myelomonocytic cells expressing the phenotype CD31pos:Ly-6Cpos:CD11b(pos):LY-6Glow. It had been demonstrated, that central nervous system invasion is facilitated by injecting L. monocytogenes-infected bone marrow cells in comparison with free bacteria or infected spleen cells. In mice transplanted with bone marrow cells from transgenic donor mice expressing the green fluorescent protein (GFP), it has been shown, that infected myeloid GFP+ cells adhere to activated brain endothelial cells, accumulate in brain vessels and participate in the pathogenesis of meningoencephalitis and brain abscesses [11].

It was shown in an independent study [12] that more than 90% of the blood leukocytes associated with bacteria were CD11b+ mononuclear cells. Subset analysis of the monocytes according to Ly-6C expression revealed that most of the infected monocytes belonged to the Ly-6Chigh subset. These cells are comparable to CX3CR1lowCCR2+Gr-1+ blood monocytes in mice and to

CD14+CD16– blood monocytes in humans [13]. Researchers have stated that a monocyte left shift toward a predominance of less mature cells compared to those recently released from the bone marrow takes place in the course of infection. Interestingly, avirulent L. monocytogenes Δ hly mutants, which do not produce listeriolysin O and typically neither escape phagosomes nor replicate intracellularly, did not stimulate this shift. By comparison, listeriolysin O-producing Δ actA mutants, which do escape phagosomes and replicate intracellularly, but are avirulent because they lack F-actin-based motility, did elicit a subpopulation shift similar to that of wild-type bacteria [13].

Importantly, 88% of CD11b+ leukocytes which were isolated from the brains of lethally infected mice were identified as Ly-6Chigh monocytes while only a few CD11bhighLy-6Cmed-hi leukocytes were present in the brain at steady state [12]. Kinetic analysis has shown a significant influx of Ly-6Chigh monocytes into the brain 2 days after systemic infection and simultaneous up-regulation of brain macrophage chemoattractant protein-1 (MCP-1) gene expression. Considering that Ly-6Chigh monocytes correspond to the CX3CR1low/GR-1+ monocytes, which are CCR2+ and thus can be recruited by MCP-1[13], this findings testify that CNS invasion during systemic infection in mice occurs via Ly-6Chigh - facilitated trafficking [12].

In addition, some observations and experimental data indicate that L.monocytogenes is able to use several different mechanisms to invade CNS.

In vitro data show that it can invade and replicate within endothelial cells, including primary human brain microvascular endothelial cells [14,15]. L.monocytogenes possesses specific adhesins that may play roles in mediating these interactions [16] in addition to the internalin-dependent mechanisms. However, experimental data and clinical observation indicate that L.monocytogenes is not particularly tropic for the brain endothelium in the same way that they are for other cells, in particular hepatocytes. For example, after intravenous infection with high bacterial load, animals that succumb early die from peripheral organ failure but manifest little changes in the CNS [6].

Nevertheless, injection of bacteria into the carotid artery of goats produced lesions in the meninges, the ependyma of the cerebral ventricles, and the aqueduct similar to those caused by extracellular bacteria such as S. pneumoniae that produce a high-density bacteraemia during clinical infection [17]. In some experimental conditions certain level and the duration of bacteraemia ensure CNS invasion during the early phase of infection [18]. Authors have obtained an intense inflammatory reaction involving the choroid plexuses and severe meningoencephalitis characterized by multiple granulomatous foci predominantly located in the brainstem and associated with diffuse meningitis was observed by day 5 after intravenous injection of (1-2) x 106 bacteria.

But, it shoud be noticed that development of high-density bacteraemia during listeriosis in adults is possible against the background of severe life threatening lesion of peripheral organs. In experimental conditions animals with similar lesions, as it has been noted [6], die from peripheral organ failure before substantial changes in the CNS appearance. In addition it was shown that normal human serum, hypothetically the immunoglobulin G (IgG) fraction, strongly inhibit L. monocytogenes invasion of human brain microvascular endothelial cells, a process dependent on InlB in the absence of serum [19]. Although newborn serum also demonstrated inhibitory activity, it was approximately 50-fold less potent than the same concentration of adult serum. This finding is consistent with the extreme susceptibility of the neonatal CNS to invasion by L. monocytogenes and, at the same time, doesn't confirm an assumption that direct invasion of brain microvascular endothelial cells during bacteraemia plays a significant role in the establishment of CNS infection in adults.

The third route of CNS invasion, infection via neural transport, was explored more then 50 years ago by Asahi et al. [20]. Injection L.monocytogenes into the oral membranes of mice and goats, or feeding the animals with abrasive food that had been soaked in bacterial cultures, in 72% and 65% cases respectively cause development of the brain stem encephalitis 6 days after infection. Examination of the brain and cranial nerves revealed mononuclear infiltrations along the length of the trigeminal nerve from the distal end in the lips to the proximal terminus in the medulla, in addition to neutrophilic perivascular cuffing throughout the brain stem. In the goats histological analysis has revealed mononuclear infiltrates in the trigeminal nerve from the maxillary and mandibular branches to the medulla, usually with focal meningitis. These pathological findings were very similar to those for naturally occurring cases of L.monocytogenes encephalitis in sheep and goats [21, 22, 23]. The authors concluded [20] that transport of L. monocytogenes from the oral cavity to the brain stem via the trigeminal nerve was the likely mechanism by which CNS disease was established in ruminants.

Subsequent studies using electron microscopy identified intra-axonal bacteria in cases of spontaneous L. monocytogenes encephalitis in sheep [21, 22]. The role of bacterial transfer along a neural route in brain stem encephalitis or transverse myelitis pathogenesis was confirmed by numerous experimental data. It was shown that rhombencephalitis developed ipsilateral to the site of L. monocytogenes injection into the facial muscle and the cut end of the facial nerve, whereas transverse myelitis followed injection into the triceps sura muscle and the cut sciatic nerve [24]. Myelitis could be prevented by surgical disruption of the sciatic nerve proximal to the site of bacterial injection. Furthermore, bacteria could be identified in axons and within mononuclear cells in the peripheral nerve fascicles.

Despite the susceptibility of neurons for infection with L. monocytogenes no species-specific tropism for neurons was shown in brain cell cultures experiments. In murine [26] and ovine [27] fetal brain cell cultures bacteria was predominately internalized by CD68-positive macrophages. Astrocytes, oligodendrocytes, and fibronectin-expressing cells were infected to a lesser extent. The lowest rates of infection are observed in neurons.

Thus the most probable sequence of events in the neuronal route of CNS invasion is (i) rapid uptake of bacteria from oral tissues by tissue macrophages or recruited to the site of damage monocytes; (ii) following spread to distal ends of nerves that form branches of the trigeminal ganglion; (iii) afferent movement through the trigeminal ganglion into the brain stem with subsequent cell to-cell spreading and development of the focal neuronal lesion [1].

This mechanism of infection is clearly important in ruminants, in which L. monocytogenes-contaminated silage

has been linked to epidemics of encephalitis [23, 24]. The relevance of the neuronal route in humans is less clear taking into account lacking of the abrasive qualities in foodstuffs linked to human listeriosis.

Whether inflammatory disease in oral cavity or dental caries could be a contributing factor in humans is not known, but some data are indicative of certain possibilities. For example experimental inoculation of the L. monocytogenes into the dental pulp of sheep cause the brain stem encephalitis developed on the same side as the dental infection [28]. In addition, listerious brain steam encephalitis developed frequently in previously healthy young adults [29-31]. That fact suggests that Listeria monocytogenes is able to exploit dissemination way inaccessible for wholly competent immunity.

In conclusion we have emphasize a strong possibility that significance of L.monocytogenes in human pathology in industrialized countries will increase owing to appearance of a vulnerable population of immunocompromised individuals, and the concomitant development of large-scale agro-industrial plants and refrigerated food.

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LISTERIOUS INVASION OF THE CENTRAL NERVOUS SYSTEM
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Listeriosis is life threatening food-related infection with systemic dissemination of causative agent and multiple organs lesion. Although L.monocytogenes is wide spread in the environment, listeriosis is uncommon illness in the general population. The most vulnerable groups are neonates, pregnant women, elders and patients with impaired cell-mediated immunity. A failure of the immune system to control peripheral infection substantially increases the risk for the cerebral involvement. The latter ensures severe and often irreversible consequences. In addition, the cases of listerious brain steam encephalitis in previously healthy immunocompetent young adults have been described. Unlike extracellular bacteria, that commonly invades CNS with primary meningeal lesion, L.monocytogenes infection results in a variety of CNS manifestations including meningitis, meningoencefalitis, encephalitis and abscesses in the brain or spinal cord. Diversity of clinical and pathological signs is determined by multiple factors, but substantially reflects causative agent life style features and different abilities to entry to the CNS that are ensured by this features. The extensively raising published experimental data array on this topic highlight some patterns of relationship which is crucial for pathogenesis understanding.
Key words: listeriosis, infection, meningitis, encephalitis

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ЛІСТЕРІОЗНА ІНВАЗІЯ ЦЕНТРАЛЬНОЇ НЕРВОВОЇ СИСТЕМИ
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Лістеріоз – потенційно летальна харчова інфекція, для якої характерна системна диссемінація збудника з поліорганними ураженнями. Незважаючи на широку розповсюдженість L.monocytogenes в оточуючому середовищі, лістеріоз достатньо рідке в загальній популяції захворювання. До найбільш вразливих категорій належать вагітні жінки, новонароджені, особи похилого віку та пацієнти з дисфункцією клітинної ланки імунітету. Нездатність імунної системи контролювати інфекцію в периферичних органах суттєво підвищує ризик ураження центральної нервової системи з важкими, у багатьох випадках незворотними наслідками. Крім того, опубліковані дані про випадки лістеріозного стовбурового енцефаліту у імунокомпетентних молодих осіб. На відміну від типових бактерійних збудників інфекцій ЦНС, що не є внутрішньоклітинними патогенами та вражають в першу чергу менінгеальні структури, L.monocytogenes здатна забезпечити первинну маніфестацію у формі менінгіту, менінгоенцефаліту, енцефаліту, абсцесів головного або спинного мозку. Варіабельність клінічних та патоморфологічних проявів визначається багатьма факторами, що впливають на перебіг інфекційного процесу, однак, головним чином, відображує особливості стиля життя збудника і різноманітні можливості щодо ураження ЦНС, забезпечувані цими особливостями. Екстенсивно зростаючий масив опублікованих експериментальних даних в межах цієї тематики дозволяє створити уявлення про закономірности, принципово важливі для розуміння патогенезу лістеріозного ураження ЦНС.
Ключові слова: лістеріоз, інфекція, менінгіт, енцефаліт

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ЛИСТЕРИОЗНАЯ ИНВАЗИЯ ЦЕНТРАЛЬНОЙ НЕРВНОЙ СИСТЕМ
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Листериоз – потенциально летальная пищевая инфекция, для которой характерна системная диссеминация возбудителя с множественными органными поражениями. Несмотря на широкую распространённость в окружающей среде L.monocytogenes, листериоз достаточно редкое в общей популяции заболевание. К наиболее уязвимым для этой инфекции категориям относятся новорожденные, беременные женщины, пожилые люди и пациенты с дисфункцией клеточного звена иммунитета. Неспособность иммунной системы

контролировать инфекцию в периферических органах существенно увеличивает риск поражения центральной нервной системы с тяжелыми, часто необратимыми последствиями. Кроме того, описаны случаи развития листериозного стволового энцефалита у иммунокомпетентных лиц молодого возраста. В отличие от типичных бактериальных возбудителей инфекций ЦНС, не являющихся внутриклеточными патогенами и поражающими в первую очередь менингеальные оболочки, L.monocytogenes способна обеспечить первичную манифестацию в форме менингита, менингоэнцефалита, энцефалита, абсцессов в головном или спинном мозге. Многообразие клинических и патоморфологических проявлений является следствием воздействия комплекса факторов, влияющих на инфекционный процесс, но, главным образом, отражает особенности стиля жизни возбудителя и разнообразие путей системной диссеминации, которые этими особенностями обеспечиваются. Экстенсивно растущий массив опубликованных экспериментальных данных в рамках этой тематики, позволяет создать представление о закономерностях, принципиально важных для понимания патогенеза листериозного поражения ЦНС.
Ключевые слова: листериоз, инфекция, менингит, энцефалит