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The Infectious Disease of the Immunocompromised Host and the Elderly: Listeriosis

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Abstract

Listeria monocytogenes is an uncommon cause of illness in the general population. However, this bacterium is an important cause of severe infections in neonates, pregnant women, the elderly, transplant recipients, and other patients with impaired cell-mediated immunity. Various clinical features due to *L. monocytogenes* have been described such as sepsis, central nervous system infections, endocarditis, gastroenteritis and localized infections. A review of the clinical aspects of listeriosis with emphasis on the elderly with underlying diseases and immunosuppressive therapy, is given in this paper.

Introduction

Clinical features of human listeriosis include self-limiting gastroenteritis in outbreak cases, spontaneous abortion in pregnant women, and severe infections (sepsis and meningitis) in immunocompromised persons and the elderly. In the latter, the case-fatality rate is 20%-30%. The incidence of nonpregnancy-associated listeriosis has increased recently in Europe despite strict food regulations. In Centers for Disease Control and Prevention (CDC)'s recent nationwide surveillance report, most listeriosis cases occurred among adults aged ≥ 65 years [1-3].

Listeriosis, usually is a mild disease in pregnant women, but it can cause severe outcomes for the fetus or newborn infant. There is a growing interest for the investigation of food-borne listeriosis outbreaks [1]. *Listeria monocytogenes*, being the only human pathogen among *Listeria* species [4,5], it has the potential for life-threatening invasive infections in elderly persons, immunosuppressed transplant recipients, and others with impaired cell-mediated immunity [1,4-6]. It is important that practicing immunologists and geriatricians are to be familiar with the non-specific and differing clinical aspects of this uncommon disease.

Clinical Aspects of Listeriosis

The predisposing factors of listeriosis

Listeriosis is mainly a food-borne zoonotic infection. The elderly is at high risk for listeriosis, but symptoms are non-specific and diagnosis is difficult. The intracellular life-cycle of *Listeria* protects the bacterium from host innate and adaptive immune responses [6,7]. Antibiotic treatment requires agents able to penetrate, distribute, and remain stable within host cells. *Listeria* activates T-cell mediated immunity which under the influence of cytokines, attracts macrophages that produce inflammatory granulomata where bacteria are destroyed. Memory T-cells provide an acquired resistance to *Listeria* infection, and this might explain why listeriosis is linked with malignancy, immunosuppressive therapy, AIDS, pregnancy and the neonate [7].

For most high-risk conditions, the risk for infection was higher among older patients. The epidemiology of listeriosis in England and Wales changed during 2001-2008; more patients ≥ 60 years of age had bacteremia than in previous years. For serious infection with *L. monocytogenes* malignancies accounted for more than one third of conditions and cancer patients had a 5-fold increased risk for development of listeriosis. Cancers of the blood seemed to have the greatest ratio. Other high-risk conditions included diabetes mellitus; alcoholism; certain diseases of the circulatory system and the musculoskeletal system and connective tissue; noninfective enteritis and colitis; and diseases of the liver and kidney. Authors have pointed out that physicians should consider a diagnosis of listeriosis when treating patients who have concurrent conditions [8].

Apart from the immune status of the host, other factors which influence whether or not invasive disease occurs include the virulence of the infecting strain and the size of the inoculum. The infective dose is unknown, but is estimated to be between 10^4-10^6 organisms/g of ingested product, although this estimate might be lower in groups at risk [7], and a high inoculum of ~10^9 is required to produce disease in healthy mammals [6,9]. Most often, *Listeria* are transmitted via the ingestion of contaminated food. Unpasteurized dairy products, such as raw milk and soft cheeses, and preprocessed foods are reported to be especially associated with listerial infection. Iron is an additional virulence factor for *L. monocytogenes,* and clinically, iron-overload states are risk factors for listerial infection [6,9].

Clinical approach to listeriosis

The duration of the incubation period of listeriosis is unknown, but is likely to be about 31 (11-70) days [6]. Some studies demonstrate that the listeriosis incubation period is shorter than generally assumed and varies according to the clinical form of the disease. Not surprisingly the shortest incubation period is observed for listeria

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associated gastroenteritis (one day). The incubation period is also short for bacteraemia cases, with a median of 2 days and is longer for central nervous system (CNS) cases, with a median of 9 days ($p < 0.05$). These observations suggest that CNS involvement occurs after transient bacteraemia and thus has a longer incubation period [10]. Clinical syndromes described for *L. monocytogenes* infection in adults are discussed in the text. Central nervous system infections and bacteremia or sepsis-like syndrome are the most frequently observed clinical presentations [6,9,11,12].

Bacteremia or sepsis without a localized infection is most common in compromised hosts. The patient often appears severely ill with fever, nausea, vomiting and malaise. Sepsis may progress to disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), and multi-organ system failure. The clinical features of listerial sepsis are similar to other types of bacterial sepsis and its diagnosis is based on a positive blood culture [6,13,14].

L. monocytogenes has tropism for the brain as well as for the meninges. Meningitis is the most frequently recognized listerial infection. Clinical syndromes due to *L. monocytogenes* in CNS are meningitis, meningoencephalitis and abscess formation [4,6].

Meningitis, with or without focal neurological signs, is the commonest form of CNS listeriosis. Clinical features of listerial meningitis are similar to that of more common etiologic agents. The onset of infection may be acute or subacute. The clinical picture is usually characterized by high fever, nuchal rigidity, movement disorders such as tremor and/or ataxia, and seizures. Seizures are seen more commonly than in other types of meningitis. The most common non-meningitic form of CNS listeriosis is encephalitis, involving the brainstem, of which infection is named rhombencephalitis. Patients with listerial meningoencephalitis have subacute onset of illness that is characterized by focal neurological findings in the hindbrain, including ataxia and multiple cranial nerve abnormalities. Fever may be absent or unnoticeable in 15% of cases [6,13,15,16].

Analysis of cerebrospinal fluid (CSF) may show a negative Gram stain, pleocytosis, increased protein and normal glucose concentration. CSF culture positive for *L. monocytogenes* may develop late, and blood cultures may reveal the organism first. Eighteen of 32 cases were diagnosed with CNS infection. Of these, nine cases could be evaluated on the basis of the results of CSF analysis. Mononuclear cell predominance was observed in three of nine cases with listerial meningitis [6,13,17].

L. monocytogenes may also be present within brain abscesses in about 10% of cases when the CNS is involved. Abscesses are particularly likely to occur in the immunosuppressed population, and the subsequent mortality rate is quite high. Twenty-five percent of patients also have meningitis, and almost all patients become bacteremic [6,13].

Listerial endocarditis is observed in about 8% of infected adults. It occurs on both native and prosthetic valves. Listeria has been found to preferentially infect left-sided valves and is often a source of systemic bacterial emboli. The mortality rate for listerial endocarditis is approximately 50%. The patients who are diagnosed with listerial endocarditis should be evaluated for an underlying gastrointestinal tract pathology including cancer [6,13].

In a healthy population, consumption of food contaminated with *L. monocytogenes* usually causes self-limiting febrile gastrointestinal disease presenting with nausea, vomiting and diarrhea. Several outbreaks of febrile gastroenteritis have demonstrated that *L. monocytogenes* can cause typical food-borne gastroenteritis. Patients become ill within 24-48 h of exposure to the contaminated food. This disease should be considered when stool cultures are negative in a patient with acute gastroenteritis. In a few instances, gastroenteritis leads to invasive listeriosis [6,13,14].

L. monocytogenes causes not only systemic disease, but also localized infections. Direct inoculation of the organism results in conjunctivitis, skin infection and lymphadenitis. Listerial bacteremia can lead to the development of peritonitis, cholecystitis, hepatitis, pleuritis, splenic abscesses, pericarditis, osteomyelitis, and endophthalmitis. These localized infections can be seen as the result of septic emboli with listerial endocarditis. Patients having localized listerial infections usually suffer from underlying diseases [4,6,13].

Complications of invasive disease including disseminated intravascular coagulation, adult respiratory distress syndrome, and rhabdomyolysis with acute renal failure have been documented. Rare episodes of reinfection have occurred [6].

Diagnosis requires isolation of *L. monocytogenes* from normally sterile clinical specimens (CSF, blood, joint fluid, and so forth) and identification through standard microbiologic techniques. In clinical specimens, the organisms may be gram-variable and look like diphtheroids, cocci, or diplococci. Laboratory misidentification as diphtheroids, streptococci, or enterococci is not uncommon, and the isolation of a "diphtheroid" from blood or CSF always should alert one to the possibility that the organism is really *L. monocytogenes* [6].

Management of listeriosis

There have been no controlled trials to establish a drug of choice or the duration of therapy for listerial infection. Most of the experience of treating *L. monoctogenes* is with the use of ampicillin, penicillin and amoxicillin and to date, no bacterial resistance to penicillin has been detected. Ampicillin is generally considered the preferred agent, although its superiority to penicillin is questionable. Carbapenems demonstrate delayed in vitro bactericidal activity (48 hours) at levels that are obtainable in the CSF as with ampicillin [6,7].

For those intolerant to penicillins, trimethoprim-sulfamethoxazole as a single agent, is thought to be the best alternative. *In vitro, L. monocytogenes* has a wide range of antibiotic sensitivities but is resistant to cephalosporins, clindamycin, and chloramphenicol. Cephalosporins are ineffective against *Listeria* because they do not bind to bacterial penicillin-bound protein-3 (PBP3). Gentamicin and tobramycin have been reported to have greater *in vitro* activity than the other aminoglycosides. There is limited experience with quinolones and rifampicin although they show in vitro activity. Listerial resistance to vancomycin is rare, and its use (though limited) has been employed in endocarditis, as well as in listerial meningitis (in which cerebral intraventricular injections were administered) [6,7].

Treatment of listeriosis requires collaboration with an infectious diseases specialist. Meningitis doses should be used for all patients, even in the absence of CNS or CSF abnormalities, because of the high affinity of this organism for the CNS. Relapses and treatment failures are reported in those with meningitis treated for less than 2 weeks; therefore, treatment for 3 weeks is recommended for all cases of meningitis. Bacteremic patients without CSF abnormalities can be treated for 2 weeks. Patients with rhombencephalitis or brain abscess should be treated for at least 6 weeks and followed with serial magnetic resonance imaging studies (or computed tomography scans). Endocarditis should be treated for 4 to 6 weeks No data exist concerning antimicrobial efficacy in listerial gastroenteritis; the illness is self-limited, and treatment is not warranted [6].

Clinical experience with listeriosis

Authors presented three listeriosis cases with various clinical manifestations which the diagnosis was difficult [18]. Those three cases (Table 1) which appeared in two consecutive months (second case two days after the first case and the third one 40 days after), could have not been diagnosed as listeriosis, if *L. monocytogenes* growths from blood cultures had not been reported from clinical microbiology laboratory of the hospital [18]. The bacteria was confirmed as *Listeria monocytogenes* serotype 4b by the Institute of National Enteric Pathogens Laboratory, Ankara.

Conclusion

Listeriosis is a rare disease with increasing incidence occurring mainly in elderly people and patients suffering from underlying

Table 1: Clinical and laboratory features of three listeriosis cases followed at a teaching and research hospital.

Demographic data Case (Age/Gender)	**Case 1** (74/F)	**Case 2** (66/F)	**Case 3** (77/F)
Underlying diseases (Pre-Medications)	Diabetes mellitus Decompensated heart failure Chronic obstructive lung disease	Diabetes mellitus Decompensated heart failure Rheumatoid arthritis (Corticosteroid therapy)	Diabetes mellitus Idiopatic trombocytic purpura (Corticosteroid therapy)
Consciousness	Blurred conscious	Unconscious	Unconscious
Clinical syndromes	Sepsis Acute renal failure Hepatitis	Sepsis Cardiac rhythm disorder Pneumonia	Sepsis ARDS DIC Hepatitis Brain abscess
Laboratory data	WBC 8200/mm^3 Hb 11.8/mm^3 PLT 225000/mm^3 Bun 324 mg/dL Creatinin 2.8 mg/dL INR 1.7 CK 2500 U/L ALT 439 U/L AST 267 U/L T. Bilirubin 3.1 mg/dL	WBC 2700/mm^3 Hb 6.2/mm^3 PLT 45000/mm^3 Bun 57 mg/dL Creatinin 1.4 mg/dL INR 1.1 CK 699 U/L ALT 16 U/L AST 35 U/L	WBC 36100/mm^3 Hb 10.8/mm^3 PLT 36000/mm^3 Bun 35 mg/dl Creatinin 1.2 mg/dL D-Dimer 6337 µgFEU CK 122 U/L ALT1435 U/L AST 520 U/L T. Bilirubin 2.3 mg/dL PCO_2 22.3 mmHg PO_2 52.6 mmHg
Outcome	Exitus (First day)	Exitus (Third day)	Recovery

diseases and immunosuppressive therapy, and it should be considered an emerging health problem.

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